"FORMULATION AND IN VITRO EVALUATION STUDIES ON ORAL DISINTEGRATING TABLETS OF AMBROXOL HYDROCHLORIDE BY USING NATURAL SUPER DISINTEGRANTS"

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This is to certify that the works embodied in this dissertation entitled **"*FORMULATION AND IN VITRO EVALUATION STUDIES ON ORAL DISINTEGRATING TABLETS OF AMBROXOL HYDROCHLORIDE BY USING NATURAL SUPER DISINTEGRANTS*"** submitted in the partial fulfillment for the degree of **MASTER OF PHARMACY** in Pharmaceutics. The Tamil Nadu Dr. M.G.R. Medical University, Chennai, is a bonafide work, which was carried out by **Mr.CHINTHAMREDDY RAVITEJA(Reg.No.261210803)** under my guidance and supervision during the academic year 2013-2014.

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DECLARATION

The work presented in this dissertation entitled **"*FORMULATION AND IN VITRO EVALUATION STUDIES ON ORAL DISINTEGRATING TABLETS OF AMBROXOL HYDROCHLORIDE BY USING NATURAL SUPER DISINTEGRANTS*"** was carried out by me under the guidance of, **Mrs.S.CHANDRA., M.Pharm., (Ph.D).,** Assistant Professor in Department of Pharmaceutics, J.K.K.Munirajah Medical Research Foundation College of Pharmacy, and Komarapalayam. This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other university.

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INDEX

1. INTRODUCTION

The oral route of drug administration is the important method of administering drug for systemic effects. Except in certain cases the parentral route is not routinely used for self administration e.g. insulin. The topical route of administration has only recently been developed to deliver drugs to the body for systemic effect. The parentral route of administration is important in treating medical emergencies in which the subject is coma or unable to swallow. Nevertheless at least 90% of all drugs used to provide systemic effect are administered by oral route. When a new drug is developed pharmaceutical company ask is whether or not the drug can be effectively administered for its intended effect by oral route of drug that are administered orally, solid oral dosage forms indicates the preferred class of product. Tablet and capsules indicates unit dosage forms in which usual dose of drug has been accurately placed[1].

Tablet is defined as solid pharmaceutical dosage form containing drug substance with or with out suitable excipients and prepared by either compression or molding method. They have been widely used since the later part of the 19th century, and their popularity continues. The term compressed tablet is believed to have been used by wyeth and brother of Philadelphia. During this same period, molded tablet were introduced to use as hypodermic tablets for the preparation of solution for injection. Tablet remains popular as a dosage form because of the advantages both to the manufacturer (e.g. simplicity and economy of preparation, stability, and convenience in packing, shipping and dispensing) and patient (e.g. accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Although the basic medicinal approach for their manufacture has remained the same, tablet technology has gained great improvement. Effect are being made continually to

understand more clearly the physical characteristics of powder compaction and the factor affecting the bioavailability of the drug from the dosage form after oral administration[1,2].

Although tablets frequently are discoid in shape, they were also available in round, oval oblong, cylinder or triangular shape. They may differ greatly in size,shape and weight depending on the amount of the drug substance present and the intended method of administration. They are divided into two classes by whether they are made by compression or molding. Compressed tablets usually are prepared by large- scale production method, while molded tablets generally involve small- scale production method. Tablet formulation and design may described as the process where the formulator ensures that the current amount of the drug in the right form is delivered at or over the proper time at the proper rate and in the desired location, while having its chemical integrity protected to that point. Most recently, new concept and federal regulations being made on bioavailability and bioequivalence and on validation are influencing on tablet formulation, design and manufacture[2].

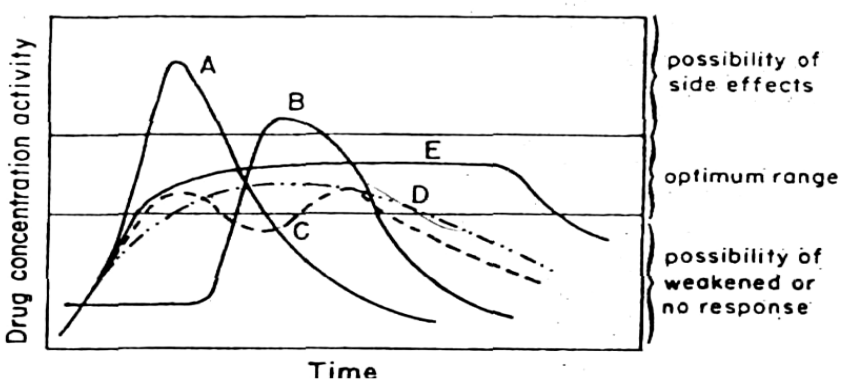


Fig No.1: Relationship between drug concentration or activity and time, for products possessing various release profiles. A, immediate release; B, Delayed action; C, Repeat action; D, Prolonged release; E, controlled; sustained release.

1.1 Types of tablets[1]

- Compressed tablet
- Multi compressed tablet
    - Layered tablet
    - Compression coated tablet
- Repeat action tablet
- Delayed action and Enteric coated tablet
- Sugar coated tablets
- Chewable tablets
- Buccal tablets
- Sublingual tablets
- Troches and Lozenges
- Dental cones
- Implantation tablets
- Vaginal tablets
- Effervescent tablets
- Dispersible tablets
- Hypodermic tablets

Tablets used in the Oral Cavity

The tablets under this group are aimed release API in oral cavity or to provide local action in this region. They avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

a) Lozenges and troches

b) Sublingual tablet

c) Buccal tablet

d) Dental cones

e) Mouth dissolved tablet

Tablets Administered by Other Routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

a) Vaginal tablet

b) Implants

Tablets used to prepare Solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used.

a) Effervescent tablet

b) Hypodermic tablet

c) Soluble tablet

1.2 Tablet Properties

Tablets can be made in any shape, although requirements of patients and tableting machines mean that most are round, oval or capsule shaped. More unusual

shapes have been manufactured but patients find these difficult to swallow, and they have more manufacturing problems.

Tablet diameter, size and shape are determined by the machine tooling used to produce them - a die cavity, upper and a lower punch were required. This is called an station of tooling. The thickness is determined by the amount of tablet material and the position of the punches used during compression. Once this is done, we can measure the corresponding pressure applied during compression. The shorter the distance between the punches, thickness, and the greater the pressure applied during compression and the harder the tablet. Tablets need to be hard enough that they don't break up in the bottle, friable enough that they disintegrate in the gastric medium.

The tablet is composed of the Active Pharmaceutical Ingredient (active drug) and with various excipients. These are biologically inert ingredients which enhance the therapeutic effect or are necessary to design the tablet. The filler or diluents (e.g. Lactose, mannitol or Sorbitol) were bulking agents, providing a quantity of material which can accurately be formed into a tablet. Binders (e.g. methyl cellulose,starch or gelatin) hold the ingredients together so that they can form a tablet. Lubricants (e.g. magnesium stearate, talc or polyethylene glycol) were added to reduce the friction between the tablet, punches and dies so that the tablet compression and ejection processes are in smooth. Disintegrants or superdisintegrants (e.g. starch or cellulose) are used to promote wetting and swelling of the tablet so that it breaks up in the gastrointestinal medium; this is necessary for the dissolution of API. Superdisintegrants are sometimes used to increase the speed of disintegration of tablet. Additional ingredients may also be added such as coloring agents, flavoring agents and coating agents for the development of tablet. Formulations which are

designed using small quantities in a laboratory machine called as Powder Compaction Simulator machine[3].

1.3 Choice of Excipients

The selection of excipients in tablet formulations depends on the API, the type of tablet, the desired characteristics, and the manufacturing process used. Several types of tablets were available in the market. They include prompt release, from which the drug dissolves in a very short time (sublingual or buccal tablets), and immediate release and modified release, which includes most of the oral administered tablets that were swallowed. Other types include effervescent, bilayered, chewable, multiple compressed tablets and tablets for solution. The particular characteristics of a tablet may be achieved by adding colors, pigments, flavours, sweeteners and a sugar or film coating. The types of excipients selected for a formulation depend on the basic process used to manufacture the tablets[4].

1.4 Drug-Excipient Interactions and Their Effect on Absorption

Excipients were traditionally used as an inert substances but they can have tremendous impact on the pharmacological activity of a drug substance when added to a formulation. The effect will depend on the characteristics of the drug and on the quantity and properties of the excipients used. Excipients were classified according to the formulation, although many excipients perform multiple functions. Diluents allow the formulation of a tablet and can form large proportion by weight of a formulated product when the active ingredient is very potent. The physical characteristics of the diluents play an important role; for example, triamterene was shown to dissolve more rapidly when it was formulated with hydrophilic fillers such as lactose and starch as

compared with insoluble diluents. Disintegrants swell when wetted and are added to a formulation to facilitate the breakdown of the dosage form into granules and powder particles. The newer disintegrants, called superdisintegrants, provides an extremely rapid break up of a tablet owing to their ability to swell to many times of their original size. Wicking and swelling were primary mechanisms of actions for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas etc., may play a role in tablet disintegration. Co processing is defined as combining or more established excipients by an appropriate. Coprocessing of excipient could lead to formation of excipients with major properties compared with the simple physical mixtures of their components or with individual components. A large number of coprocessed diluents are commercially used. The representative examples are Ludipress, Cellactose and starlac. The use of co-processing is totally unexplored avenues in disintegrants. The widely used super disintegrants are Sodium Starch Glycolate, crospovidone and croscaramellose sodium were used as super disintegrants have strengths and weakness.

1.5 Excipients used in tablets

Excipients are inert substances used as diluents or vehicles for a drug. Various diluents or fillers, binders or adhesives, disintegrates, lubricants, glidants or flavours, fragrances and sweeteners were used as excipients.

They must meet certain criteria as follows

- They must be physiological inert substances.
- They must be acceptable to regulatory authorities.
- They must have physic chemical stability

- They must be free of micro organisms considered to be harmfull or otherwise objectionable.
- They should not be interfering with the bioavailability of the drug.
- They must be commercially available and should have purity according to pharmaceutical standards.
- Cost must be inexpensive.
- They should meet all current regulatory requirements.
- To assure that no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the excipients and must consider compliance of each ingredient with existing standards and regulatory requirements.
- The drug-excipients and excipient-excipient interactions should be carried out in preformulations studies.

1.5.1 Fillers

Fillers are comprise a heterogeneous group of substances. Since they often forms the bulk of the tablet, selection of a candidate from this group as a carrier for a drug is of primary importance.

Eg: lactose, mannitol, dicalcium phosphate anhydrous.

1.5.2 Binders

Binders are the adhesives that holds powders together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for that bonding together for the granules under compaction to form tablet.

The quantity used and the method of using must be carefully regulated, since the tablet must remain intact when swallowing and then release its medicaments.

Binders are either sugar or polymeric materials the latter fall into two classes Natural polymers such as starches or gums include acacia, tragacanth and gelatin. Synthetic polymers such as PVP methyl cellulose and ethyl cellulose and hydroxyl propyl methyl cellulose. Binders of both types may be added to the powder mix and the mixture wetted with water, alcohol–water mixtures are also used as solvent, or binder may be put into solution in the water, solvent and added to the powder. The other method using the solution of the binder requires much less binding material to achieve the same hardness than if added dry.Mostly used binders are gelatin, glucose, methyl cellulose, acacia, starch paste, povidone, alcohol, PVP in water, PVP in alcohol and sorbitol in water

1.5.3 Lubricants

Lubricants are used in tablet formulation for the ejection of the tablet from the die cavity, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies during compression. They function by interposing a film of low shear strength at the interface between the tablet and die cavity and the punch surface. Lubricants must be carefully selected for efficiency and for the properties of the tablet formulation.

In selecting a lubricant, the following should be considered:

Lubricants reduce the bonding properties of many excipients. Over blending is one of the main causes of lubrication problems during the formulation. Lubricants should be added last to the granulation and blended for 10 min.

Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100-300 mesh screen before use in formulation.

Commonly used lubricants are magnesium stearate, talc, starch.

1.5.4 Disintegrants

Disintegrants are used in tablet preparation to break the tablet rapidly. But some of the disintegrants are also having property of enhancing solubility of insoluble dosage forms

Examples

Crospovidone: Crospovidone is disintegrant it also enhances solubility of drug.

Sodium starch glycollate: sodium starch glycollate is widely used in oral pharmaceuticals and as a disintegrant in capsule formulation.

Sodiumcrosscormellose

1.5.5 Glidants

Glidants are materials that are used to improve the flow characteristics of granules by reducing the inter particulate friction during processing in proper amounts they also serve to assure smooth and uniform flow of granules.

1.5.6 Desired criteria for mouth dissolving drug delivery system

Mouth dissolving tablet should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allows the manufacture of tablet using conventional processing and packaging equipment at low cost.

The several advantages of fast dissolving dosage forms are

1. Ease of administration for patients, those who are not co-operative.
2. Quick disintegration and dissolution of the dosage form.
3. Can be swallowed without water.
4. Allows high drug loading.
5. Can be designed to lave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.

1.6 Super disintegrants in immediate release tablets

A disintegrant were added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid medium. This is especially important for immediate release products where rapid release of drug substance is required. A disintegrant can be added to a powder mix for direct compression , wet granulation or encapsulation . While there are some tablets fillers such as starch microcrystalline cellulose which helps in disintegration, there are referred to as superdisintegrants.

1.6.1 Method of Addition of Disintegrants

The requirement placed on the tablet disintegration should be clearly defined. The ideal disintegrant has,

- Good solubility.
- Poor gel formation.
- Good hydration capacity.
- Good molding and flowing properties.
- No tendency to form complexes with other excipients.

Disintegrants are widely added to tablet granulation for the compressed tablet to break or disintegrate when placed in aqueous environment.

There are two methods of incorporating disintegrating agents into tablets:

- Internal addition method
- External addition method
- Partly internal and external methods

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In internal addition method, the disintegrant is mixed with other powders before wetting the powder mixture with the granulating

fluid. Thus the disintegrant is incorporated within the granules. When these methods are used part of the disintegrants are added internally and part externally. This provides immediate dispersion of the tablet into previous compressed granules while the disintegrating agents within the granules produce further erosion of the granules to the original powder particles. The two stepped method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

1.7 Tablet processing

Pharmaceutical products are processed all over the world using the direct compressing, wet granulation, or dry granulation method. Method is chosen depend on the ingredients individual characteristics like flow property, compressibility. Choosing a method required through investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can applied.

1.7.1 Direct compression[1]

Direct compression name implies compressing tablets directly from powdered materials without modifying the physical nature of the material itself. Direct compression is generally done for the crystalline material having good physical properties required for formulation of good tablets. Main advantage of direct compression is it saves time when compared to another method of compression like wet granulation.

Advantage:

- Low labor in put
- Drying process
- Fewest processing steps

Limitations:

- Differences in densities and particle size cause stratification, which may lead to content uniformity problem of low dose drugs.
- Large dose drugs which are not easily compressible by it could require an amount of diluents so large that the resultant tablet is costly and difficult to swallow (API usually restricted to 30% of a direct compressible formula).
- Because of dry nature compression static charge build up can occur.

1.7.2 Factors to be considered for directly compressible excipients:

Flowability

Press speed requires powder to be very fluid, a property commonly referred to as product flow ability. Good flow characteristic are necessary because the mechanical action of the table press requires a volume of fill and this volume fill represent the actual tablet weight. Thus the powders in the formula must possess a consistent particle- size distribution and density to attain proper flow and achieve volume of fill.

Compressibility

Compressing a tablet of different powder that have varying physical characteristic can be difficult. If the formula has some of both characteristics larger

particles with high moisture content and small, dry particles then the tablet may or may not compress well and probably will have difficulty holding together.

Directly compressible materials are preprocessed or found naturally in the granular state. The reduced number of processing steps required by directly compressible material allows for less equipment and shorter process time comparison with wet or dry granulation processes.

1.8 Wet granulation[1,3]

Mostly widely used and most general method of tablet preparation is by wet granulation method. Wet granulation forms the granules by binding the powders together with an adhesion instead of by compaction. The wet granulation technique is done by adding a solute, suspension or slurry containing binder this can be aqueous or non aqueous which is added to the dry mix powder. The surface tension forces and capillary pressure are primarily responsible for initial granules formation. The main advantage is it meets the requirements of tablet formulation and main disadvantage is it requires many steps in process, which is time consuming.

1.9 Dry granulation[1,2]

The dry granulation process is used to form granules without using a liquid solution, this type of process is recommended for products, which are sensitive to moisture and heat. Forming granules without moisture requires compacting and densifing the powder. Dry granulation can be done on a tablet press slugging tooling. On large-scale roller compactor commonly referred to as a chilsonator. The compacted mass is called slugs and the process is known as slugging. The slugs are

screened or milled to produce a granular form of tablet materials, which have the good properties then original powder mixture.

The main advantage of granulation is it requires less equipment and eliminates the addition of moisture and the application of heat, as found in wet massing and dry steps of the wet granulation method.

1.10 Other technologies

The other technologies used for manufacturing of water dispersible tablets are as follows

- Freeze drying
- Moulding
- Sublimation
- Spray drying
- Mass extrusion

1.11 Patented technologies

- Zydus technology
- Oroslov technology
- Durasolv technology
- Wow technology
- Flash tab technology
- Flash dose technology
- Oraquick technology

In present work, an attempt was made to explore the use of Natural gums for both masking taste and as super disintegrating agents.

The advantages of such tablets will be that the patient can swallow the tablets in the form of a liquid as they disintegrate quickly when in contact with saliva[4]. The bitter taste of the drug cannot be felt with correct selection of ion exchange resin, drug resonates comes into contact with the acidic environment of the stomach, the complex is broken down quickly and completely[15]. The drug is released form the resinate directly into solution and then absorbed in the usual way.

Such tablets may also be used dispersible tablet, which will be of value in pediatric patients and those who are not co-operative.

Various techniques used for preparing mouth dissolving tablets[15] are by freeze drying, moulding, sublimation, spray drying, mass-extrusion and by direct compression. Patented technologies for mouth dissolving tablets are zydis technology durasolv technology, ora solv technology, flash dose technology, wow technology and flash tab technology.

Freeze drying :

A process in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation.

Moulding:

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depend whether and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or micro particles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution.

Sublimation:

Compressed tablets composed of highly water soluble excipients as tablet material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly. Inert solid ingredients {ex: urea, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure.

Spray-Drying:

Highly porous and fine powders can be produced by spray drying, as the processing solvent is evaporated rapidly during spray drying. For fast dissolving tablets, they developed formulation by using mannitol as bulking agent, hydrolysed and non-hydrolysed gelation as support matrix, sodium, starch glycolate as disintegrant and acidic material (ex.citric acid) and/or alkali material (ex.$NaHCO^3$) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 seconds).

Mass-Extrusion:

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

Direct Compression:

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and / or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.

Disintegrants have major role in the disintegration and dissolution process of mouth dissolving Tablets made by direct compression. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature.

The understanding of disintegrant properties and their effect on formulation has advanced during last few years, particularly regarding so called **super disintegrants.**

Disintegration efficiency is based on force equivalent concept, which is the combined measurement of swelling force development and amount of water absorption. Force equivalent expresses the capability of disintegrant to transform absorbed water into swelling force. The optimization of tablet disintegration was defined by means of disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to disintegrant concentration and above that disintegration time remains approximately constant or even increases.

Zydis Technology:

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength.

Durasolv Technology:

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consists of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into

conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

Orasolv Technology:

Orasolv technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

Flash Dose Technology:

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets. Flash dose tablets consists of self binding shearform matrix termed as “floss”. Shearform matrices are prepared by flash heat processing.

Wowtab Technology:

Wowtab technology is patented by Yarnanouchi Pharmaceutical Co. Wow means “Without water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

Flashtab Technology:

Prographarm laboratories has patented the Flashtab technology. Tablets prepared by this system consists of an active ingredient in the form of microcrystals. Drug microgranulesmay be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion. All the processing utilized conventional tableting technology.

1.12 Tablet Trouble Shooting[1]

Table No 01: Tablet Trouble Shooting[1]

PROBLEMS	CAUSES	REMEDY
Capping & Lamination	Granulation too dry,	Increase moisture content,
	Compression too hard,	Reduce compression pressure,
	Damaged upper punches,	Replace the tools which damaged,
	Less binders in granules,	Increase binders,
	Air present in granules which can not escape while compression,	Use tapered dies,
Chipping	Damaged punches or dies,	Replace the damage punches or dies,
		Reduce the compression speed,
	Compression too fast,	Increase the compression pressure,
	Compression too soft,	
Delayed Disintegration	Compression too hard,	Reduce the compression pressure,
		Improve the granulation,
	Over granulation,	Reduce the blending time of lubrication,
	Excess blending time of lubricants or glidant,	

Soft tablet	Granulation too dry,	Increase the moisture,
	Machine too fast,	Reduce machine speed,
	Excess lubrication,	Decrease the lubrication,
	Compression too soft,	Increase the compression pressure,
Hard Tablets	Compression too hard,	Reduce compression pressure,
	Uneven granulation,	Improve granulation,
Sticking & Picking	Compression too soft,	Increase compression pressure,
	Uneven granulation,	Improve granulation,
	More fines in blend,	Reduce moister content in granulation,
	Moister content in granules,	Use dehumidifier,
	High relative humidity,	Improve lubrication,
	Improper lubrication,	Polish the punches,
	Damage of upper punch,	Buffing the punches with lubricants,
Non Uniform Weight	Non uniform granules,	Provide uniform granules,
	Restricted free flow granules,	Add Glidant to improve the flow of granules,
	Granules sticking too lower punches,	Improve lubrication,
	Feed frame / hopper flow restricted,	Adjust the hopper to get free flow,
Black Mark On Tablets	Improper feed frame setting,	Improve feed frame setting,
	Excessive moisture,	Avoid excess moisture,
	Over sized granules,	Reduce granule size,
	Granules having black particles prior to compression,	Reduce granules size
	Lubrication or oil may be contaminating the powder,	Avoid contamination with Greece or oil,
Collar formation	Too much fines,	Reduce fines,

Dissolution	Large granules,	Reduce granules size,
	Tablet too hard,	Reduce tablet hardness,
	Excess lubrication,	Reduce compression hardness.

Choice of Mucolytic agents[5,6]

- Choice of mucolytic agent depends on
- Availability
- Efficacy
- Safety
- Cost

Guaphenesin, diphenhydramine are probably the most widely used Mucolytic agents

1.14 Dispersible tablet[1,6]

Definition:- Dispersible tablet are uncoated tablet that produce a uniform and immediate dispersion in water. They should disintegrate with in three minutes and produce a uniform dispersion and passes through seive no:22 when dispersed in water. Dispersible tablet are formulated for pediatric and geriatric use or for patients who has difficulty in swallowing tablets.

The chief advantage is quicker absorption and onset effect. They are generally prepared for geriatric or pediatric patients or those who are having difficulty in swallowing tablets. They dissolve in mouth with in few seconds to minutes

1.14.1 Ideal characteristics of dispersible tablets[5]:-

- Should easily disintegrate and dissolves in water
- Masks and overcome unacceptable taste of drug.
- They should have high drug loading capacity.
- They should have pleasant feel in mouth during administration.
- They should have negligible or no residue in oral cavity after administration of dosage form.
- They should have low sensitivity against environment conditions like moisture, temperature, humidity and other environmental conditions.
- Easy administration for mentally ill, disabled and uncooperative patients.

1.14.2 Advantages of dispersible tablets[1,7]:-

- Little water is required to swallow the dosage form which is highly convenient feature for patients who are travelling and do not have access to water.
- Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- Rapid disintegration and absorption of drug, which will produce quick onset of action after administration.
- Quick absorption from the GIT improves bioavailability and reduces unwanted effect caused by the drug .E.g. gastro intestinal irritation caused by NSAIDS and also improve patient compliance.
- Drug and dosage form stability should achieve.

1.14.3 Disadvantages of dispersible tablets[1,7]:-

- Most fast disintegrating tablet lack the mechanical strength common to traditional tablet. Many products are very lightweight and fragile requiring them to be individually packaged in separate conditions. Patients should be advised not to push these tablets through the foil film, but instead, peel the film back to release the fast-dissolving tablet.
- Due to the formulation of fast disintegrating tablets which also more susceptible to degradation via temperature and humidity. Some of the newest fast disintegrating tablet formulation is dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such formulation to ensure they are not exposed to high level of moisture or humidity. Excess handling of tablets can introduce enough moisture to initiate dissolution of the tablet matrix.

1.14.4 Mechanism of super disintegrants

- Because of heat of wetting
- Swelling
- Porosity and capillary action
- Due to disintegrating particle/particle repulsive forces
- Due to deformation
- Due to release of gases

1.15 Drugs to be promising in corporated in dispersible tablets

Analgesics and anti inflammatory agents -

Paracetamol, diclofenac, lornoxicam, piroxicam, aceclofenac, ibuprofen, naproxen, ketoprofen,phenylbutazone, nimesulide.

Anthelmintic –

Piperazine, albenbazole, metronidazole, thiabendazole, niclosamide.

Anti coagulants –

Heparin, warfarin, phenindione, ancrod,danaparoid, acenocoumarol,ethyldascoumacetate, lepirudin

Antiepileptics –

Lomotrigine, phenobarbitone, phenytoin, primidone, carbamazepine, valproic acid, diazepam, gabapentin, zonisamide, tiagabine, clobazam

Anti gout drugs –

Probenecid, allopurinol, sulfinpyrazone

Anti hypertensive drugs –

Furosemide, enalapril, captopril, losartan, telmisatran, verapamil, propranolol, atenolol, carvedilol, terazosin, clonidine, methyl dopa, hydralazine, sodium nitro prusside, ramipril, candesartan, diltiazem, nifedipine, amlodipine, metoprolol

Anti malarials –

Cloroquine, amodiaquine, mefloquina, quinine, quinidina, pyrimethamine, sulfadoxine

Antifungal –

Clotrimazole, miconazole, econazole, ketoconazole, voriconazyle, itraconazole, fluconazole, oxiconazole, benzoic acid, undecylenic acid, tolnaftate, butenafine, sodium thiosulfate

Anti thyroid –

Propylthiouracil, methimazole carbimazole, perchlorates, thiocyanates, iodine, organic iodide

Sedatives and hypnotics –

Phenobarbitone, butobarbitone, thiopentone, diazepam, flurazepam, nitrazepam, lorazepam, clobazam, clonazepam, zopiclone, zolpidem, zaleplon, oxazepam, alprazolam

Cardiac inotropic agents –

Digoxin, dobutamine, dopamine, amrinone, furosemide, hydralazine, bisoprolol, metaprolol, spironolactone, carvedilol, nitroprussude, milrinone

Diuretics –

Furosemide, torasemide, hydrochlorothiazide, clopamide, benzthiazide, hydroflumethiazide, metolazone, atetazolamide, mannitol, isosorbide, glycerol, spironolactone, amiloride, triamterene, xipamide, indapamide, bumetanide

Anti parkinsonian –

Levodopa, cabidopa, benserazide, ropinirole, pramipexole, selegiline, tolcapone, entacapone, amantadine, biperiden, procyclidine, orphenadrine, promethazine

Gastro intestinal agents –

Ranitidine, cimitidine, roxatidine, famotidine, omeprazole, rabeprazole, pantoprazole, lonsoprazole, oxyphenonium, misoprostol, sodium bicarbonate, magnesium hydroxide

Anti histamines -

Levocetirizine, cetirizine, fexofenadine, clemastine, cyclizine, mebhydroline, chlorpheniramine, meclizine, buclizine, hydroxyzine, promethazine, diphenhydramine, dimenhydrinate, montelukast

Hypolipidaemic drugs –

Lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin, clofibrate, fenofibrate, bezafibrate, gemfibrozil, nicotinic acid, ezetimibe, gugulipid

Nitrates and other angina drugs –

Glyceryl trinitrate, isosorbide dinitrate, erythrityl tetranitrate, propronolol, atenolol, metoprolol, varapamil, nifedipine, nimodipine, felodipine, amlodipine, benidipine, lacidipine, nicorandil, dipyridamole, ranolazine, trimetazidine, oxyphedrine

Opioid analgesics –

Morphine, codeine, thebaine, papaverine, noscapine Other drugs such as proteins, peptides, recombinant drugs, sex hormones stimulants, neuro muscular agents were also used in the preparation of the dispersible agents

Local anesthetics –

Procaine, chloroprocaine, prilocaine, lidocaine, tetracaine, bupivacaine, ropivacaine, dibucaine, cocaine, benoxinate, oxethazaine, benzocaine

1.16 Commercially available various dispersible tablets

Table no -2 Commercially available various dispersible tablets

Trade name	**Active ingredient**
Feldene fast melt	Piroxicam
Claritin redi Tab	Loratidine
Maxalt MLT	Rizatriptan
Zyprexia	Olanzepine
Pepcid RPD	Fomotidine
Zofran ZMT	Ondensetron
Zooming ZMT	Zolmitriptan
Zelaper TM	Selegilline
Tempra quicklets	Acetaminophen
Febrectol	Paracetamol
Nimulid MDT	Nimesulide
Torrox MT	Rotecoxib
Olanex instab	Olazapine
Romilast	Montelukast
Banedryl fast melt	Diphenhydramine pseudoephedrine

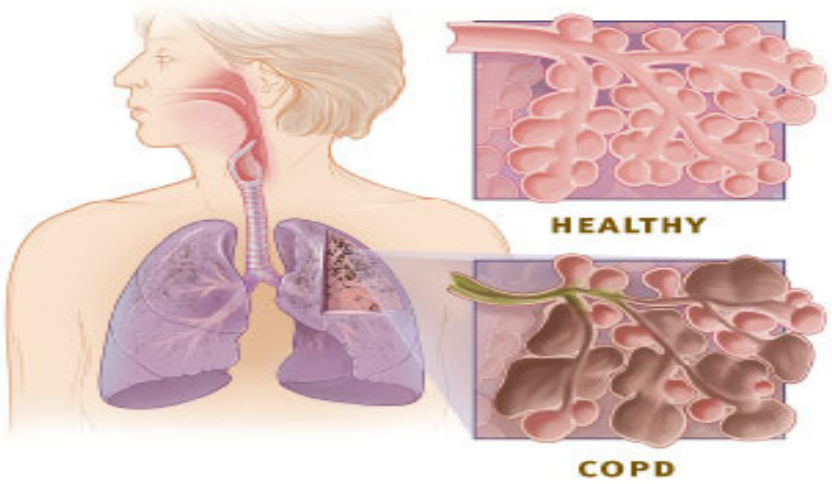
1.17 DISEASE PROFILE

1.17.1 Chronic Obstructive Airway Disease

Chronic obstructive airway disease is a chronic diffuse irreversible inflammatory airflow obstruction of lungs. This leads to a limitation of the flow of air to and from the lungs causing shortness of breath (FSK Barar 2000).

- COAD includes two main diseases:
  - Chronic bronchitis
  - Emphysema
- Alternative term include COPD & COLD.

Fig No 2: Healthy alveoli and COPD affected Alveoli.



1.17.1.1 Epidemology

- In UK 30000 death per year due to COPD, 12% hospitalized.
- Incidence of COPD in smokers is 15%.

- In US 10.2 millions have COPD.
- Incidence of COPD in non smokers in is 5%.

1.17.1.2 Ethiology

- Smoking : - Increased smoking increases the chance of COPD.
- AGE : - Increase in age results in ventilatory impairment.
- Gender : - Both male and female has the possibility.
- Occupation: - Workers in coal, gold mining, cement etc has the possibility.
- Genetic factors: - deficiency in α_1 antitrypsin, tissue necrosis etc.
- Air pollution: - increase in urban areas than rural areas.

1.17.1.3. Classification

Two main types:

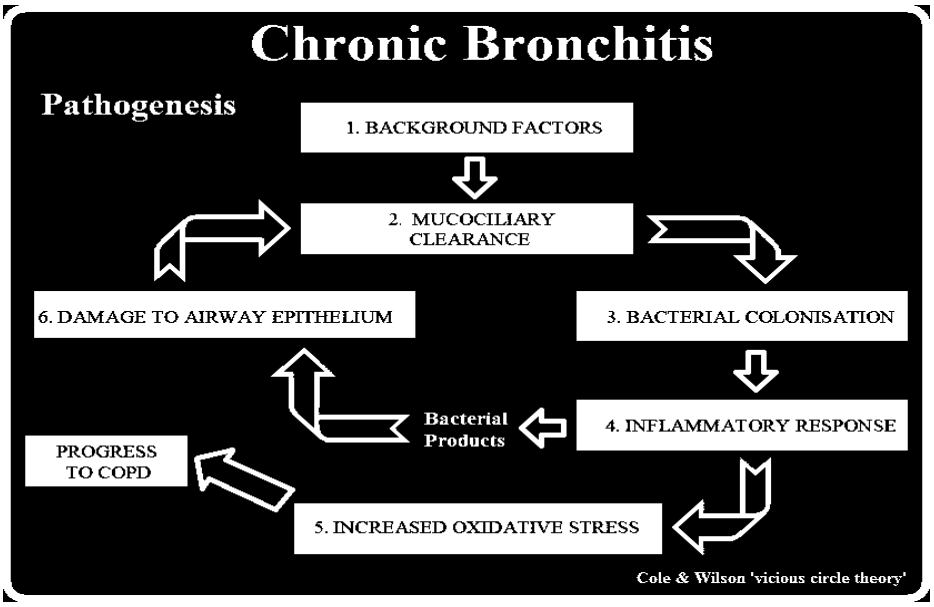
- Chronic Bronchitis.
- Emphysema.

1.17.2. Chronic Bronchitis

Chornic bronchitis is a condition of excessive mucus production by tracheobronchial tree which results in air way obstruction due to edema and bronchial inflammation.

Bronchits is considered chronic because cough produce more than 30ml of sputum in 24hrs for atleast 3 months of the year for the two consecutive years.

Fig No 3: Chart showing the progress of COPD



1.17.2.1. SIGNS AND SYMPTOMS

- Cough.
- Sputum production.
- Frequent infections.
- Intermittent dyspnea.
- Oedema.
- Plethora (excess of blood).
- Cyanosis.
- Wheezing.
- Diminished breath sound.

1.17.2.2 Diagnosis

- **Sputum Inspetion**
    - Thick mucopurulent sputum.
    - Microscopic analysis detect neutrophills and micro organisms.

- **Blood Analysis**
    - Polycythemia due to erythropoiesis.
    - Increased WBC count due to bacterial infection.
- **Pulmonary Function Test**
    - Normal in early disease stage.
    - Later increase in RV, decrease in FEV.
- **Chest Cardiograph**
    - Lung hyperinflation.
    - Increased broncho vascular marking.
- **ECG**
    - Right ventricular hypertrophy.

1.17.2.3. Pathophysiology

There are two pathological process underlying development of chronic bronchitis.

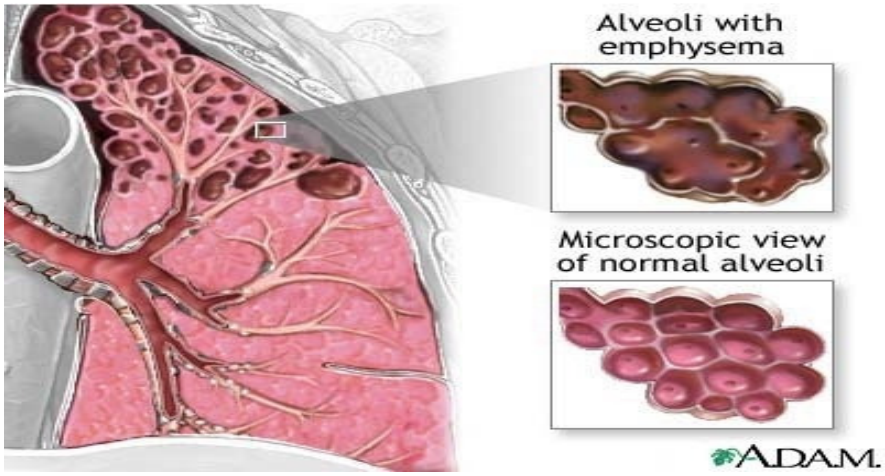
A) Hypersecretory disorder characterized by expectoration with increasing susceptibility to respiratory infections. Hypersecretion of thick and viscous mucus leads to distension of alveoli and loss of gas exchange function. Accumulation of pus and infected mucus lead to chronic viral and bacterial infections.

B) Alveolar distension and destruction results in distortion of blood vesels closely associated with alveoli lead to increase in BP in pulmonary circulation.

1.17.3. Emphysema

It is defined as a permanent change in the anatomy of lungs with enlargement and destruction of the alveoli and respiratory bronchioles that result in deterioration in gas exchange and impared ventilation (Paul L. Munson 2001).

Fig No 4: Healthy alveoli and Emphysema affected alveoli.



1.17.3.1. Signs and Symptoms

- Minimal cough.
- Scant sputum.
- Dyspnea.
- Weight loss.
- Occational infections.
- Barrel chest.
- Diminished breath sound.

1.17.3.2. DIAGNOSIS

- **Sputum Inspection**

- Scanty sputum.
- Infections are less frequent than in chronic bronchitis.

- **Blood Analysis**

- Decreased AAT level.

- **Pulmonary function Test**

- Normal or increased static lung compliance, decreased FEV, increased TLC and RV.

- **Chest cardiograph**

- Lung hyperinflation.
- Flattened diaphragm
- Vertical heart.
- Decreased vascular marking in lungs.

1.17.3.3. Pathophysiology

- Loss of available gas exchange surface leads to increase in dead space and impared gas exchange.
- Loss of elastic recoil in small airways leads to a tendancy to collapse particularly during expiration and increase thoracic gas volume and hyperinflation of lungs.

Two types

- Centrilobular emphysema: - destruction of respiratory bronchioles, alveolar ducts and alveoli.
- Panacinar emphysema: - due to α_1 – antitrypsin deficiency.

1.17.4 Pharmacological Treatment (K.D. Tripathi 2008)

A) Prophylactic Treatment

- Single dose of pneumococcal vaccine.
- Annual influenza vaccination.

B) Broncho dialators

- **β2 agonist**
- Short acting: Albuterol, Levabuterol.
- Long acting: Salmetrol, Furmeterol.
- **Anti cholinergics**
- Short acting: Ipratropium bromide.
- Long acting: Tiotropium bromide.
- Methyl Xanthines**:** Theophylline.

C) Mucolytics

- Bromhexine, Ambroxol HCl, Iodinated glycerol.

D) Cortciosteriods

- Systemic : Hydrocortisone, Prednisolone.
- Inhalation: Beclomethasone dipropionate, Budesonide.

E) Expectorants

- Guaiphenesin.

F) Antibiotics

- 2^{nd} Genaration cephalosporin: Cefuroxime, Cefactor.
- β Lactum: Amoxicillin.

- Macrolides: Azithromycin.
- Oral fluoroquinolone: Ciprofloxacin, Gatifloxacin.

G) Antioxidants

- N- acetyl cysteine

1.17.5 Broncho Pulmonary Disease

Ambroxol is indicated as "secretolytic therapy in broncho pulmonary diseases associated with abnormal mucus secretion and impaired mucus transport. It promotes mucus clearance, facilitates expectoration and eases productive cough, allowing patients to breathe freely and deeply. A sustained release dosage form with 75 mg to be given once a day. Ambroxol is also available as dry powder sachets, inhalation solution, drops and ampoules as well as effervescent tablets (Michael Curtis Michael Walker etal 2006).

1.17.6 Sore Throat

Ambroxol also provides pain relief in acute sore throat. Pain in sore throat is the hallmark of acute pharyngitis. Sore throat is usually caused by a viral infection. The infection is self limited and the patient recovers normally after a few days. The patient experiences continuous pain in the throat when swallowing. The main goal of treatment is to reduce pain. The main property of Ambroxol for treating sore throat is the local anaesthetic effect (Alexander Schutz, Hans-Jürgen Gund etal 1993).

1.17.7 Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is characterized by the presence of copious eosinophilic, periodic acid Schiff (PAS)-positive material in the alveoli and

by an excess of surfactant components (both lipids and proteins) in lung lavage. It may be present during the neonatal period or later in life. PAP is the consequence of a genetic defect involving the lungs, such as a mutation of the surfactant protein B (SP-B) gene, or it can represent an aspect of a different genetic disease, such as lysinuric protein intolerance. The main pharmacodynamic effects of ambroxol hydrochloride are surfactant stimulation, mucokinetic activity and some secretagogue activity (Karl, 1987). The lung surfactant system is a mixture of phospholipids and protein synthesized and secreted in the alveolar spaces primarily by type II pneumocytes. So type II pneumocyte stimulation with ambroxol hydrochloride can lead to chemico-physical and functional changes in alveolar macrophages, probably through an increase in surfactant secretion and uptake (Luisetti et al., 1987). Thus an oral ambroxol hydrochloride and therapeutic BAL should be the first choice in treating PAP (Hisashi Suyama, Naoto Burioka etal 1999).

2. REVIEW OF LITERATURE

1. **Milind p wage, et al (2010)** Prepared fast dissolving tablet of aceclofenac by direct compression method after incorporating superdisintegrants croscarmellose sodium, crospovidone and sodium starch glycolate. Nine formulation having superdisintegrant at different concentration (10, 15, 20 mg) level were prepared. Effect of superdisintegrant on wetting time, dispersion time, drug content and in vitro release has been studied.The result of the study shows that tablet containing cross carmellose sodium showed excellent in vitro dispersion time and drug release as compared to other formulation.

2. **Anupama kalia, et al (2009)** Formulated mouth-dissolving tablets of oxcarbazepine by using two different technologies, direct compression method and solid dispersion technology. Tablets produced by direct compression method contain crospovidone as a superdisintegrant and aspartame as a sweetener. Solid dispersions of oxcarbazepine with polyvinylpyrrolidone K-30 and polyethylene glycol 6000 in different weight ratios were prepared with a view to increase its water solubility.The result of the study shows that Oxcarbazepine solid dispersions with polyvinylpyrrolidone K-30 in 1:2 ratios of drug: carrier showed maximum drug release and hence, compressed along with other excipients into mouth dissolving tablet.

3. **Sandeep B. Pathi, et al (2009)** Formulated Olanzapine quick dispersing tablets by direct compression method. Effect of super disintegrant crospovidone on wetting time, disintegration time, and drug content and in vitro release has been studied. A 32 factorial design was employed in

formulating a quick dispersible tablet. The selected independent variables crospovidone and hydroxypropylcellulose showed significant effect on dependent variables i.e. disintegration time and percent drug dissolved.The result of the study shows that disintegration time and percent drug dissolved decreased with increase in the level of crospovidone. The similarity factor f2 was found to be 72.68 for the developed formulation indicating the release was similar to that of the marketed formulation.

4. **Snehalatha,etal(2009)**Formulated Lornoxicam dispersible tablets using natural disintegrants which would release the drug rapidly with predetermined rate. Six batches of Lornoxicam dispersible tablets were prepared by using various natural disintegrating agents in order to get required theoretical release profiles. The influence of the disintegrant concentration and granulation technique on the release of Lornoxicam was studied. The study reveals that the formulation prepared by direct compression exhibits better dissolution, disintegration at low concentration of natural disintegrants.

5. **Raghavendra Raon.G,et al (2009)** Formulated chlorthalidone fast dissolving tablet by direct compression using cogrinding and solid dispersion methods by using chlorthalidone as a model drug. Chlorthalidone is a well known diuretic used in the treatment of hypertension and edema. The half life of chlorthalidone is 40 hours. The major problem with this drug is erratic absorption from GIT, limited aqueous solubility and a high melting point, which may hinder dissolution causing decreased bioavailability of the drug. Therefore the solid dispersions and cogrinding method were followed with a

view to increase solubility and bioavailability.The result of the tablet formulation containing polyvinyl pyrrolidone K-12 solid dispersion showed maximum drug release than the chlorthalidone polyvinyl pyrrolidone K-12 co-grinding method. The dissolution profile of best solid dispersion formulation was compared with co-grinding method formulation.

6. **Biraju Patel, et al (2009)** developed fast dissolving tablets of glipizide were prepared by direct compression method with a view to enhance patient compliance. Two superdisintegrants viz, crospovidone and croscarmellose sodium (4%, 5%, 6%) with different binders viz, pvp k-30 and pregelatinized starch (3%) were used. The prepared batches of tablets were evaluated for hardness, friability, and weight variation, disintegration, wetting time, drug content and in vitro dissolution studies. Based on evaluating parameters, Formulation prepared by using 5% croscarmellose sodium with 3% PVP K30 was selected as optimized formulation. Finally, the optimized formulation was compared with marketed conventional formulation.

7. **Jashanjit Sing, et al (2009)**formulated and optimized an orodispersible formulation of meloxicam using a 22 factorial design for enhanced bioavailability. The tablets were made by non-aqueous wet granulation using crospovidone and mannitol. A 22 factorial design was used to investigate the amount of crospovidone and taste masking, soothening hydrophilic agent (mannitol), as independent variables, and disintegration time as dependent response. Formulated orodispersible tablets were evaluated for weight

variation, friability, disintegration time, drug content, wetting time, water absorption ratio and in vitro drug release.

8. **P.S. Zade, et al (2009)** formulated, evaluated & optimized fast dissolving tablet of Tizanidine Hydrochloride using Eudragit E 100 as a taste masking agent. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with three super disintegrants e.g. sodium starch glycolate, crosscarmellose sodium and crospovidone. The blend was examined for angle of repose, bulk density, tapped density and hausner's ratio. The tablets were evaluated for hardness, drug content and friability and disintegration time.The result concluded that these tablet disintegration in oral cavity was also tested and was found to be 22 sec. Other tablets were prepared by using camphor as sublimating agent. It was concluded that tablets prepared by addition of superdisintegrant has less disintegration time than those prepared by sublimation method.

9. **NG Raghavendra Rao, et al (2009)** studied the developed the fast dissolving tablets of poorly soluble carbamazepine by the direct compression technique with β -cyclodextrin complexes using various super disintegrants like Indion-414, croscarmellose sodium, crospovidone and sodium starch glycolate. The result of the formulation shows excellent rate of absorption and/or the extent of bioavailability for such a poor soluble drug is controlled by rate of dissolution in gastrointestinal fluids. Hence, to enhance the solubility of the drug, a complex of carbamazepine was prepared with β -cyclodextrin and this complex was compressed into tablets.

10. **Parmar R.B., et al (2009)** formulated and evaluated the Domperidone, an antiemetic drug, has been used as an add-on treatment in adults and children. As precision of dosing and patient's compliance become important prerequisite for quick relief from emesis, there is a need to develop a formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while traveling and better compliance. Hence, the present research work was held to develop a fast dissolving tablet of domperidone, prepared with Avicel PH 102 and Sodium Starch Glycolate by direct compression method.The result of the studies shows an effective, pleasant tasting formulation was found to have a good hardness of 3 kg/cm2, disintegration time of 27+1 seconds and in vitro drug release of not less than 95% within 30 minutes. The drug release was found to be comparable with the marketed dispersible tablet.

11. **S Furtado, et al (2008)**studied the development and characterization Orodispersible tablets of famotidine were prepared using camphor as subliming agent and sodium starch glycollate together with crosscarmellose sodium as superdisintegrants. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, in vitro and in-vivo dispersion, mouth feel and in vitro dissolution.The result of the formulations showed low weight variation with dispersion time less than 30 seconds and rapid in vitro dissolution. The results revealed that the tablets containing subliming agent had a good dissolution profile. The drug content of all the formulations was within the acceptable limits of the United States Pharmacopoeia XXVII.

12. **C Mallikarjuna Setty, et al (2008)**developed the aceclofenac fast-dispersible tablets have been prepared by direct compression method. Effect of superdisintegrants (such as, croscarmellose sodium, sodium starch glycolate and crospovidone) on wetting time, disintegration time, drug content, in vitro release and stability parameters has been studied. The result revealed that the disintegration time and dissolution parameters ($t_{50\%}$ and $t_{80\%}$) decreased with increase in the level of croscarmellose sodium. Whereas, disintegration time and dissolution parameters increased with increase in the level of sodium starch glycol ate in tablets. However, the disintegration time values did not reflect in the dissolution parameter values of crospovidone tablets and release was dependent on the aggregate size in the dissolution medium.

13. **Shishu, et al (2008)** prepared chlorpheniramine maleate rapid disintegrating tablet in saliva. Bitter masked granules were prepared using aminoalkyl methaarcylate copolymer (Eudragit E-100) by extrusion method.

    The result revealed that In vitro release at pH 6.8 indicate that perceivable amount of drug will not be realeae in saliva while percentage release (more than 80% in 30 min) obtained at acidic pH 1.2 stomach. These taste masked granules having sufficient strength of 3.5 kg/cm were evaluated.

14. **Mukesh Gohel, et al (2004)** developed mouth dissolve tablets of nimesulide. Granules containing nimesulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The porous granules were then compressed.

Alternatively, tablets were first prepared and later exposed to vacuum. The tablets were evaluated for percentage friability, wetting time, and disintegration time. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of camphor and a higher percentage of crospovidone.The result revealed that the sublimation of camphor from tablets resulted in superior tablets as compared with the tablets prepared from granules that were exposed to vacuum. The systematic formulation approach helped in understanding the effect of formulation processing variables.

15. **S. Khalil, et al (2000)** compared Lornoxicam and tenoxicam selective membrane sensors. The construction and general performance characteristics of potentiometric plastic-membrane sensors for Lornoxicam and tenoxicam drug-anions are described. The electroactive materials are based on ion pair complexes with aliquot 336S cation. Both electrodes show near Nernstian response over the range 10−2–10−5 mol/l, with a detection limit of about 2.4_10−6 mol/l for Lornoxicam and 6_10−6 mol/l for tenoxicam. The selectivity of the electrodes to a number of organic and non-organic anions is reported. The electrodes proved useful in the determination of the active ingredient in their respective pharmaceutical preparations. The method is simple, rapid and does not require prior sample pre-treatment.

16. **Yunxia B, et al(1999)** developed a disintegrating tablets prepared by the wet compression granules under low compression force and then drying the resulting wet mass in a circulating-air oven (wet compression method).

Lactose with various particle sizes was used as the incipient, and water was used as a wetting agent. The effect of drying time, compression force, size of lactose particles, and moisture content of wet granules on tablet properties indicated that the formation and disintegration time of tablets were related to the effect of the formation of solid bridges between lactose particles. The result shows that by optimizing compression force, size of lactose particles, and moisture content of the granules, tablets meeting tensile strength greater than 0.5 Map and disintegration time shorter than 15 s were obtained by the wet compression method.

17. **Patil Pradeep S et al (2013)** Oral disintegrating tablets are emerging trend in Novel drug delivery system & received increasing demand & popularity due to ease of administration & better patient compliance .In recent years superdisintegrant have been employed to develop effectual mouth dissolving tablet & to overcome limitation of conventional tablets .In present study attempt was made to compare to disintegrating efficiency of natural superdisintegrats .Main aim of using oscimum basilicum as natural superdisintegrant was to achieve quick onset of action ,increases water uptake with short wetting time & decreasing disintegration time by cost effective direct compression method. 3 preliminary batches were prepared & these are evaluated for precompression parameter like angle of repose, carr`s index & post compression parameters like wetting time, water absorption ratio,in vitro disintegration. Hardness, friability of all formulations found within limit. Best formulation F2 batch had shown good hardness, friability, disintegration time,

swelling time. Present study revealed that mucilage obtained from oscimum basilicum was effective for their disintegrating property.

18. **Patni Sonal D et al (2013)** prepared fast dissolving tablets of Salbutamol sulphate by direct compression method for better patient compliance and immediate action in asthma. The tablets were prepared by using synthetic superdisintegrants (Croscarmellose sodium and Sodium starch glycolate) and natural superdisintegrant (mu cilage of Plantago ovata and Plantago ovata husk powder) at different concentrations as 2, 4, 6, 8 and 10 %. The Plantago ovata mucilage was extracted from the seeds of Plantago ovata (Plantaginaceae).The tablets were characterized for weight variation, hardness, friability, disintegration time, wetting time, water absorption ratio, drug content and in vitro dissolution tests. The Drug excipients compatibility study was performed by DSC and IR spectroscopy and no incompatibility was found. The tablets were subjected for accelerated stability study at 40°C /75% RH and were found to be stable. The results clearly shows Natural superdisintegrants requires less disintegration time as compared to synthetic superdisintegrants. Hence present study reveals that the fast dissolving tablets prepared by using mucilage of Plantago ovata and husk powder of Plantago ovata as superdisintegrants having better appearance and rapid disintegration time.

19. **Vikas Sharma et al** Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route. Recently researcher developed the fast disintegrating

tablets with improved patient compliance and convenience. Fast disintegrating tablets are solid dosage forms which dissolve rapidly in saliva without chewing and additional water. Fast disintegrating tablets overcome the disadvantages of conventional dosage form especially dysphagia (difficulty in swallowing) in paediatric and geriatric patients. Natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and widely available. They can also be modified in different ways to obtain tailor- made materials for drug delivery systems and thus can compete with the available synthetic excipients. With the increasing interest in polymers of natural origin, the pharmaceutical world has compliance to use most of them in their formulations.

20 **Vikas Sharma et al (2012)**Formulated fast dissolving tablets of Carvedilol by using various natural superdisintegrant like Plantago ovata, Lepidium sativum, Fenugreek and Guar gum. A Direct compression method was used to prepare fast dissolving tablets containing Carvedilol as a model drug using natural superdisintegrants. Prepared formulations were evaluated for Precompression parameters such as micromeritic properties like angle of repose, %compressibility and Hausner's ratio. Tablets were also subjected to Postcompression analysis for the parameters such as weight variation, hardness, and friability, in vitro disintegration time, wetting time, drug content and in vitro dissolution study. The results concluded that amongst all formulations, the formulation prepared with mucilage of Plantago ovata showed better disintegrating property as well as the release profile than the other used natural superdisintegrant.

21 **Nitin Bansal et al (2011)**developed orally disintegrating tablets of ondansetron HCl using natural Superdisintegrants.Method:Tablets containing the drug were prepared by dry granulation method using different concentrations of superdisintegrants such as modified gum karaya, modified natural agar, crosscarmellose sodium and sodium starch glycollate. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, in vitro disintegration time and in vitro dissolution study. Results:The results showed that modified gum karaya and modified natural agar produce rapid disintegration of tablets.The optimized formulation showed acceptable physical characteristics. The optimized batch produced complete drug release within 6 minutes. The incorporation of clove oil provided additional properties such as symptomatic relief from nausea and vomiting, good mouth feel and taste masking. Kinetic analysis showed that drug release from optimized formulation was adequately described by first order release kinetics. Conclusion:Modified gum karaya and modified natural agar can be used as an alternative superdisintegrants to commonly available synthetic and semisynthetic superdisintegrants due to their low cost, biocompatibility as well as easily availability.

22. S.Vimal Kumar et al (2010) prepared the sustained release (SR) tablets of Ambroxol Hydrochloride by wet granulation method. The effect of hydrophilic matrices on the behavior of Ambroxol Hydrochloride using different polymers and their combinations. The prepared tablets were evaluated for physical characteristics such as Hardness, Thickness, Friability, Weight variation, Content uniformity and In-vitro release behavior. The drug

release from the optimized formulation was found to follow zero order kinetics. It was also found linear in Higuchi's plot. Thus the phenomenon of drug release showed that the release of optimized formulation is controlled by diffusion. It is concluded that as compare to other formulations, optimized formulation fulfilled all criteria for SR tablet dosage form.

23.O.Ramana et al (2012) investigated to develop oral controlled release matrix tablets of Ambroxol hydrochloride by melt granulation technique using hydrophilic meltable binders such as PEG 6000 and Gelucire 50/13(Stearoyl polyoxyl glycerides). The FT-IR and DSC analysis indicated the stability and compatibility of drug with excipients.The in-vitrodissolution studies of the matrix tablets prepared using only meltable binders released almost 90 % of the drug in the first 2 hours, which lead to the incorporation of HPMC K M into the 4formulations as a release retardant to control the drug release for a prolonged period of time. The formulations F3 and F6 (both containing 30% meltable binder and 20% HPMC K M) controlled the drug release over a prolonged period of time i.e. 12 hrs and exhibited drug release patterns ideal with the theoretical release profiles of Ambroxol hydrochloride. The dissolution data obtained for various formulations were fitted into zero-order, first order, Higuchi's and Peppas kinetic models and results showed that the drug release followed first order kinetics, the profiles were linear with Higuchi's plot and "n" value obtained from peppas were within 0.45 to 0.89 indicated (anomalous diffusion) the mechanism of drug release was diffusion coupled with erosion. The optimized formulations F3 and F6 showed no

change in theirin vitrodissolution profiles after storage at 25°C/60%RH and 40°C/75%RH for a period of three months indicating their stability.

24 K.V.R.N.S.Ramesh et al (2010) Extended release matrix tablets of ambroxol hydrochloride were developed employing combination of hydroxypropyl methyl cellulose and stearic acid as the matrix materials in different proportions. Tablets containing 75 mg of the drug were formulated and made by entrapping the drug in a waxy carrier and then by the conventional wet granulation method. Granules prepared were evaluated for loose bulk density, tapped density, compressibility index, Hausner ratio and angle of repose and by determining the constants from a Kawakita plot. The prepared tablets were found to be of optimum hardness, uniform weight and acceptable friability. The release was found to be dependent on the relative proportion of hydroxyl propyl methyl cellulose and stearic acid. Kinetics of the drug release data was evaluated out by employing the relevant equations of first order, zero order, Higuchi square root and Korsmeyer – Peppas. The drug release data suggested thatthe release of the drug is first order and that the drug release is diffusion controlled.

25.Abdul althaf S et al (2011) developed a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Ambroxol pellets to present it in the form of capsules (Modified release capsules). To achieve this goal various prototype formulation trails were taken and evaluated with respect to the various quality control such as dissolution, assay, acid resistance and moisture content. The active pharmaceutical ingredient Ambroxol was

subjected to preformulation study, and the results obtained with selected excipients showed good compatibility with Ambroxol. Ambroxol coated pellets were formulated by using commercially available pellets and Ambroxol coated pellets were filled by capsule filling machine. The stability ofthe capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH, 30ºC ± 2 ºC/ 65% ± 5% RH and 25±2°C/60±5% RH conditions for 1 month. Finally, after the duration, the product was analyzed for content and dissolution study. By the stability studies, the formulated Ambroxol modified release capsules and pellets proved to be stable throughout the period of the storage. The Ambroxol modified release pellets were loaded in size 4 capsules. It showed good results in formulation of stable dosage. Modified release pellets have minimum volume in size, greater surface area and more surface of disintegration time for pellets in capsules. Small volumes of pellets enter into the systemic circulation very fast. Moreover no accumulation of drug in the body occurs.

26.Anup Kumar Roy et al 2013) developed sustained release tablets .Ambroxol hydrochloride has relatively short plasma half life. The need for the administration of the drug for two to three times a day can decrease patient compliance. Sustained release formulations that would maintain plasma level for 8-12 h might be sufficient for daily dosing of Ambroxol Hydrochloride. The overall objective of the present work was to develop an oral sustained release Ambroxol Hydrochloride tablet prepared by direct compression method using hydrophilic Eudragit RSPO and RLPO alone or in combination with hydrophobic ethylcellulose polymer as rate controlling factor. All the

batches were evaluated for thickness, weight variation, hardness, friability and drug content and in vitro drug release for 12 h. The in vitro drug release study revealed that when Eudragit RSPO, RLPO and Ethylcellulose were used alone as the only retarding polymer, a sustained drug release pattern was not observed while, Combining Eudragit with ethylcellulose, the drug release pattern was observed in a sustained manner for 12 h. F7 formulation sustained the drug release for longer period of time as compared to other formulations. So F7 was selected as the best formulation. Kinetic modeling of in vitro dissolution profiles revealed that the drug release mechanism ranges from diffusion controlled to anomalous type. Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

27.Km Ariful Islam et al 2009 aimed to perform stability study of Ambroxol Hydrochloride sustained release pellets stored in different storage conditions. The drug loaded beads were prepared by Extrusion-Spheronization technology then coated with ammonio methacrylate copolymer Type A (Eudragit RL 30 D) and ammonio methacrylate copolymer Type B (Eudragit RS 30 D) at a ratio of 2:3 (8% polymer by weight on dry basis) in Fluid Bed Coater (Wurster column). Stability study of pellets was performed as capsule dosage form in Aluminium-PVDC packaging mode at room temperature, 40oC, 40o C/75%RH & 30^{o}C/70%RH for three months. After one month the shape & size of the pellets was changed in all conditions. The color of the pellets remains unchanged up to the 2nd month in all conditions except at 40 o C/75%RH and in this case some pellets become brown. But after 3rd month,

pellets become brownish in all conditions except at room temperature. At RT the color of pellets remains unchanged during the stability study. The mean drug content decreased gradually in all conditions. In acid media the initial drug release was 23% but after 1st month it was decreased to 13-15% in all conditions. In the buffer media (pH 6.8) the drug release was increased a little bit in all conditions except at 300 C/70%RH with the passes of storage time. Stability studies at 30o C/70%RH revealed consistent drug release (f2>50) throughout the stability period. The physical properties of pellets as well as the in vitro release profile of the drug was found to be a function of the different storage conditions as well as the physico-chemical nature of the polymers.

28 Bharat V. Jain et al 2013 prepared taste masked suspension of Ambroxol Hydrochloride by abating the intensely bitter taste of Ambroxol Hydrochloride. Taste abatement was done by complexing of Ambroxol hydrochloride with different Ion Exchange Resins (IER) like Tulsion 335 and Indion 214 in different ratios. The prepared suspensions were evaluated for taste, drug content, particle size, viscosity, sedimentation volume and drug release. The resonates prepared with drug- T335 ratio (1:2) at pH 8, gave maximum drug loading. Suspension containing above resinates showed more than 80% In vitro drug release within 30 min. Prepared formulation also showed good stability and can retain its palatable taste.The developed formulation was an additional advantage like simplification of manufacturing procedure and is economical.Thus, the "patientfriendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and noncooperative patients, can be successfully formulated using this technology.

3.AIM AND PLAN OF WORK

AIM

The aim of work is to formulate fast disintegrating Ambroxol hydrochloride tablet with sufficient mechanical integrity and to achieve faster disintegration for the patient convenience.

The objective of present study is:

To develop dispersible tablet by simple and cost effective technique.

Criteria for selection of work:

- To develop and evaluate the Ambroxol Hydrochloride dispersible tablet by direct compression method.
- To develop and evaluate the Ambroxol hydrochloride dispersible tablet with two different natural superdisintegrants with different concentrations.
- To study the effect of natural superdisintegrants on dispersible tablet.

PLAN OF THE WORK

The study was planned to carry out as follows

1.Procurement of drug, polymer and other excipients

2. Preparation of mixed blend of drug and excipients by using natural superdisintegrants

- Guar gum
- Karaya gum

3.Checking Drug and Excipient compatability by FTIR studies

4.Evaluation of powder mixed blend of Drug and Excipients

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner ratio

5. Compression of tablet by Direct Compression Method

6. Evaluation of compressed tablets

- Weight variation
- Hardness
- Friability
- Estimation of drug content

- Disintegration time
- Water uptake test

7. Invitro release studies using buffer

- 6.8 Phosphate buffer

8.Drug release kinetics

9.Stability studies

4.MATERIALS AND METHODS

List of drugs & excipients used for the formulation

The following drugs and excipients used to carry out the study

Table No 3: List of drugs & excipients

S.No.	Name of the material	Name of supplier
1	Ambroxol HCl	Yarrow chemicals, Mumbai
2	Guar gum	SD Fine chemicals
3	Karaya gum	SD Fine chemicals
4	Microcrystalline cellulose	Yarrow chemicals, Mumbai
5	Aspertame	Hetero chemicals,Hyderabad
6	Magnesium stearate	Thomas Baker Pvt ltd,Mumbai
7	Mannitol	Thomas Baker Pvt ltd,Mumbai

List of Equipments

The following equipments were used for the studies

Table No: 4 List of Equipments

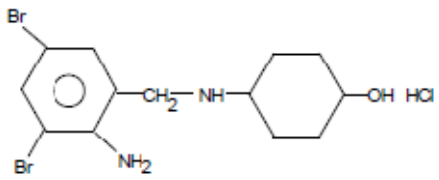
Instrument Used	Model No.	Make
FTIR Spectrophotometer	8400S	Shimadzu, Japan
UV–Visible Spectrophotometer	UV – 3000^{+}	LAB INDIA
Tablet Compression Machine	Mini Press	Rimek
Tablet Dissolution Tester USP (XXIII)	DS-8000	LAB INDIA
Tablet disintegration apparatos	N.S	Lab India
Environmental test chamber	JRIC – 11A	Oswald
Electronic Balance	AGN-303EC	AXIS
Tablet hardness tester	N.S	Monsanto
Roche's friabilator	N.S	Scientific
Hot air oven	PYROCON	York Scientific Ind., Mumbai
Digital pH meter	PHAN	LAB INDIA
Melting Point apparatus	N.S	Biotech India Ltd.

4.DRUG PROFILE

DRUG PROFILE

4.1 Ambroxol hydrochloride

Structure:



Molecular formula: C_{13} H_{18} Br_2 N_2O Hcl

Chemical name: Trans 4,2-amino-3, 5 dibromo benzy1 amino) cyclohexanol hydrochloride.

Appearance: A white or almost white crystalline powder, odourless or almost odourless.

Solubility: Soluble in methanol

N,N – dimethy1 formamide

Slightly solube in water and ethanol

Practically insoluble in chloroform and benzene.

Storage : Ambroxo hydrochloride should be protected from light.

Therapeutic category:

Expectorant: enhanced mucolytic.

Respiratory disorders:

Used in a variety of respiratory disorders including chronic bronchitis

Cystic fibrosis and infant respiratory distress syndrome. Also used in the treatment of cough.

Uricosuric action:

It also shows uricosuirc effect. The minimum effective dose of lowering plasma uricacid concentrations was found to be between 250 mg and 500mg daily given in 2 divided doses. Although these doses are much higher than those used to treat broncho pulmonary disease, doses as high as 1 gram daily were well tolerated.

Daily dose:

30 to 120 mg has been given by mouth in 2 to 3 divided doses.

Adverse effect:

Hyper sensitivity : A report of contact allergy to Ambroxol.

Mechanism of action:

Ambroxol hydrochloride is a potent mucolytic & mucokinetic, capable of including bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberatin lysosomal enzymes network of fibres in tenacious sputum is broken. It is particularly useful in if mucus plugs are present. (Tripti KD, 2003)

Pharmacokinetics:

Ambroxol hydrochloride is rapidly absorbed from the gastrointestinal tract and under goes extensive first pass metabolism in the liver. It is widely distributed to body tissues. About 85% of the drug is excreted as metabolites. It is highly found to plasma proteins. It has a terminal half life about 12hours.

Ambroxol hydrochloride crosses the blood brain barrier and small amounts cross the placenta. Administration of Ambroxol hydrochloride by mouth to healthy subjects produced peak plasma concentration after about 1 hour. Only small amounts were excreted unchanged.

Excipients Profile[15]

An ideal bulk excipient for Fast Dissolving Tablet should have the following properties

- Disperses and dissolve in water within few seconds without leaving any residue.
- Masks the offensive taste and offers a pleasant mouth feel.
- Enable sufficient drug loading and reminds relatively unaffected by changes in humidity or temperature.
- Preferably direct compressible and yield sufficiently robust tablet to with stand manufacturing, packaging and transportation, yet disperses quickly in water.

4.2. Guar Gum

Nonproprietary Names **:** BP: Guar Galactomannan

PhEur: Guar Galactomannan

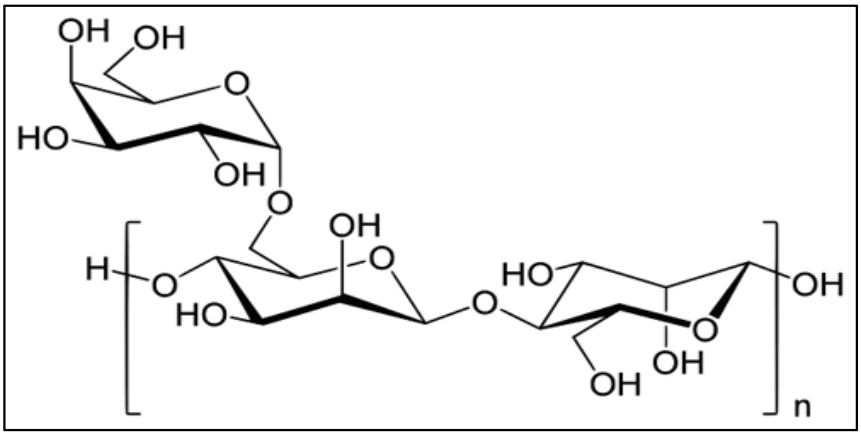
USP-NF: Guar Gum

Synonyms: Galactosol; guar flour; guar galactomannanum; jaguar gum;Meyprogat; Meyprodor; Meyprofin.

Empirical Formula **:** $(C_6H_{12}O_6)$ n

Chemical name **:** Galactomannan polysaccharide

Structural Formula:



Functional Category:

Suspending agent; tablet binder; tablet disintegrant; viscosity increasing agent.

Description:

Guar gum occurs as an odorless or nearly odorless, white to yellowish-white granules with a bland taste.

Typical Properties:

Acidity/alkalinity:pH = 5.0-7.0 (1% w/v aqueous dispersion)

Density:1.492 g/cm^3.

Solubility:

Practically insoluble in organic solvents and in cold or hot water.

Stability and Storage Conditions:

Guar gum granules should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Guar gum is compatible with most other plant hydrocolloids suchastragacanth. It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum.

Safety:

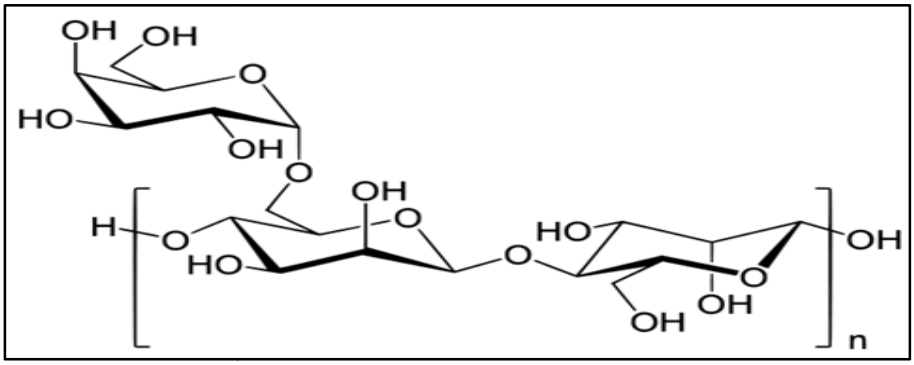
Guar gum is widely used in foods, and oral and topical pharmaceutical formulations. Excessive consumption may cause gastrointestinal disturbance such as flatulence, diarrhea or nausea (Raymond C Rowe *et al*, 2009).

4.2. Karaya Gum

Synonyms **:** Karaya, gum karaya, Sterculia, gumsterculia, Kadaya, Katilo, Kullo, Kuterra.

Empirical Formula **:** $(C_{32}H_{48}O_{14})n$

Structural formula:



Functional Category:

Emulsifier, stabilizer, thickening agent.

Description:

Unground product: It occurs in tears of variable size and in broken irregular pieces having a characteristic semi-crystalline appearance; pale yellow to pinkish brown; translucent and horny.

Powdered product: It occurs as pale grey to pinkish brown; a distinctive odour of acetic acid.

Typical Properties:

Solubility: Insoluble in ethanol, in water it swells to form a granular, stiff, slightly opalescent gel.

Loss on drying: Not more than 20% (105°C, 5 h).

Total ash: Not more than 8%

Acid insoluble ash: Not more than 1%

Applications in Pharmaceutical Formulation or Technology:

Karaya gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range.Karaya gum gels show pseudoplastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.

Stability and Storage Conditions:

Karaya gum should be stored in a well closed container in a cool and dry place.

Incompatibilities:

Karaya gum is an anionic material and is not usually compatible with cationic surfactants, polymers or preservatives, as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation ofKaraya gum from a solution.

Safety:

Karaya gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products, and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient. The estimated acceptable daily intake for Karaya gum has been set by the WHO at up to 10 mg/kg body weight.

4.3.MICROCRYSTALLINE CELLULOSE[53]

Nonproprietary Names:

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

Synonyms:

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Chemical Name:

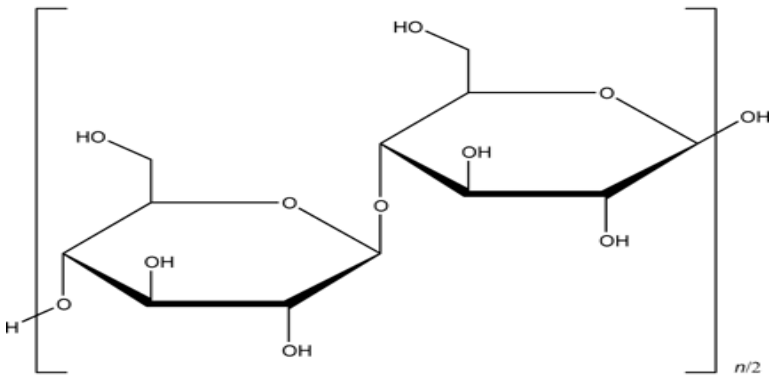
Cellulose [9004-34-6]

Empirical Formula and Molecular Weight:

$(C_6H_{10}O_5)_n$,36 000

where n is 220.

Structural Formula:



Functional Category:

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrantproperties that make it useful in tableting.

4.4. MAGNESIUM STEARATE[53]

Non-Proprietary Names

BP: Magnesium stearate; IP: Magnesium stearate

PhEur: Magnesii stearas; USPNF: Magnesium stearate

Synonyms: Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Chemical Name and CAS Registry Number: Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula: $C_{36}H_{70}MgO_4$

Molecular Weight: 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula

$[CH_3 (CH_2)_{16}COO]_2Mg$

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Physical Properties :

Crystalline Forms: High-purity magnesium stearate has been isolated as a trihydrate, a dehydrate and an anhydrate.

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Density (true): 1.092 g/cm^3

Flash point: 250°C

Flowability: Poorly flowing, cohesive powder.

Melting Range: 117–150°C (commercial samples); 126–130°C (high purity magnesium stearate).

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

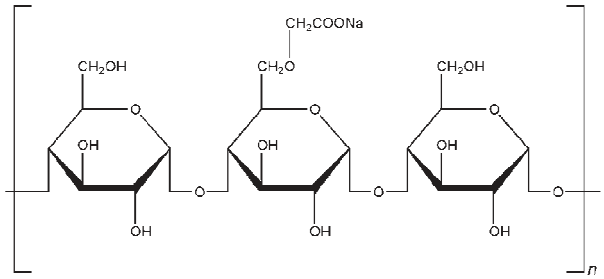
Specific Surface Area: 1.6–14.8 m^2/g

Stability and Storage Conditions: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Pharmaceutical Application

Magnesium stearate is widely used in cosmetics, food and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

4.5.Mannitol

Non-proprietary names	BP: Mannitol JP: D-Mannitol PhEur: Mannitol USP: Mannitol
Synonyms	Cordycepic acid; C*PharmMannidex; E421; Emprove; mannasugar; D-mannite; mannite; mannitolum;
Chemical name and molecular weight	D-Mannitol [69-65-8]
Empirical Formula and Molecular Weight	C6H14O6 182.17
Structural formula	
Functional Category	Diluent; plasticizer; sweetening agent; tablet and capsule diluent; therapeutic agent; tonicity agent.
Applications in Pharmaceutical Formulation	Mannitol is widely used in pharmaceutical formulations and foodproducts. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol may

be used in direct-compression tablet applications,for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryltrinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouthfeel'.

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or freeflowing granules. It has a sweet taste, as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as ortho rhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold,dilute acids or alkalisor by atmospheric oxygen in the absence ofcatalysts. Mannitol does not undergo Maillard reactions.The bulk material should be stored in a well-closed container in acool, dry place.

Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out bypotassium chloride or sodium chloride. Precipitation has been

reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/Ml concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and mayform complexes with some metals such as aluminum, copper, andiron. Reducing sugar impurities in mannitol have been implicated inthe oxidative degradation of a peptide in a lyophilized formation.Mannitol was found to reduce the oral bioavailability ofcimetidine compared to sucrose.

4.6.Aspertame

Nonproprietary Names

BP: Aspartame

PhEur: Aspartame

USP-NF: Aspartame

Synonyms :

(3S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4-oxobutanoic acid; 3-amino-N-(a-carboxyphenethyl)succinamic acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)-succinamic acid; APM; aspartamum; aspartyl phenylamine methyl ester;Canderel; E951; Equal; methyl N-L-a-aspartyl-L-phenylalaninate;NatraTaste;NutraSweet;Pal Sweet;Pal Sweet Diet;Sanecta;SC-18862;Tri-Sweet.

Chemical Name and CAS Registry Number : N-L-a-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

Empirical Formula and Molecular Weight : C14H18N2O5 294.30

Structural Formula

Functional Category : Sweetening agent.

Applications in Pharmaceutical Formulation or Technology : Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations.

It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1g provides approximately 17kJ (4kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.

Description : Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste

Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known.

Method of Manufacture

Aspartame is produced by coupling togetherL-phenylalanine (orLphenylalanine methyl ester) andL-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet aaspartame and nonsweetb-aspartame from which thea-aspartame has to be separated and purified. The enzymatic process yields only

a-aspartame.

Stability and Storage Conditions : Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation productsL-aspartyl-Lphenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine with a resulting loss of sweetness. A third-degradation product is also known, b-L-aspartyl-L-phenylalanine methyl ester. For the stability profile at 258C in aqueous buffers. Stability in aqueous solutions has been enhanced by the addition of cyclodextrins, and by the addition of polyethylene glycol 400 at

pH 2. However, at pH 3.5–4.5 stability is not enhanced by the replacement of water with organic solvents.

Methodolgy

Pre-formulation studies

Identification of Drug[1,37]:-

Organoleptic Properties:

The colour, odour and taste of the drug were recorded using descriptive terminology.

Melting Point:

Capillary tube is used to determine the Melting point.

Solubility Study:

It is important to know about solubility characteristic of a drug in aqueous system. Since they must possess some limited aqueous solubility to elicit a therapeutic response.The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia, 2007.

UV Spectrophotometric Study:

The absorption maximum of the test solution was observed between 200-400 nm region by using UV-Visible Spectrophotometer.

Compatibility study:

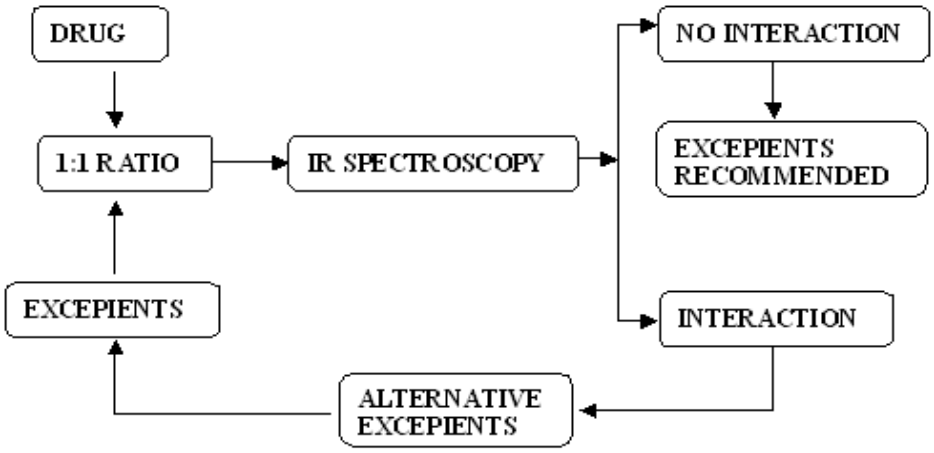
A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of paramount importance.

FT-IR:

Compatibility of the Drug with the excipients was determined by subjecting the physical mixture of the drug and the polymers of the main formulation to infrared absorption spectral analysis. Any changes in chemical composition of the drug after combining it with the polymers were investigated with I.R. spectral analysis.

Fig : 5 Schematic representation of compatibility studies



Procedure:

Weighed amount of drug (3mg) was mixed with 100mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer.

Drug–Polymer Interaction/Compatibility study using FTIR

Fourier Transfer Infrared Spectroscopy

IR has been the method of choice to probe the nature and extent of interaction in polymer blends. IR was used in the study because mixing of the two components at molecular level will cause changes in oscillating dipoles of the molecules. If the drug and polymer interact then functional groups in FTIR spectra will show band shift and broadening compared to that of pure compounds.

Method

Potassium Bromide disc containing drug, polymer and their physical mixture were prepared to record the spectrum by using Shimadzu 8400S FTIR.

Standard Calibration Curve of Ambroxol HCl

Ambroxol Hclwas quantitatively analyzed by various techniques. In the present study, Ambroxol Hcl was estimated by UV spectrophotometry method.

Determination of λ_{max} for Ambroxol Hcl

Two different stock solutions of drug sample were prepared by dissolving 100.0 mg of drug in 100.0 ml of Phosphate buffer were further diluted and analyzed spectrophotometrically to determine λ_{max}.

Observation:

The λ_{max} was found to be 246 nm.

Preparation of standard calibration curve of Ambroxol Hcl In 0.1 N HCl

A. Preparation of Phosphate buffer of 6.8 pH which is prepared by preparing stock solutions of 27.218 g of Potassium di hydrogen Phosphate in 1000ml and 0.2M NaOH i.e 8 gms of NaOH in 1000ml and adding 250ml of potassium di hydrogen Phosphate and 112 ml of sodium hydroxide stock solution and make up to 1000ml.

B. Preparation of dilutions for standard curve: Stock solution was prepared by dissolving 100.0 mg of Ambroxol Hcl in 100.0 ml of Phosphate buffer solutions, which was further diluted to give the solutions of concentration 2, 4, 6, 8 and 10 µg/ml respectively. Absorbance of these solutions were measured on UV spectrophotometer at 246 nm and plotted against the concentration to give the standard curve.

Evaluation of Mixed Blend[38]:-

Bulk Density:

An accurately weighed powdered blend from each formula is introduced in to a measuring cylinder was shaken to remove any agglomerates. The volume occupied by the powder was measured which results in determining bulk volume bulk volume. It is determined using the following formula.

$$\text{Loose bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}}$$

Tapped bulk density (TBD):

An accurately weighed powdered blend from each formula is introduced in to a measuring cylinder was shaken to remove any agglomerates.The measuring cylinder was tapped until no change in volume was noted which give the tapped volume. It is determined by using the following formula.

$$\text{Tapped bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}}$$

Hausner's Ratio:

It determined by using following formula:

$$\text{Hausner's Ratio} = \frac{\text{Tapped bulk density}}{\text{Loose bulk density}}$$

A hausner ratio less than 1.25 shows good flow while greater than 1.5 shows poor flow.

Carr's compressibility index

It is a simple index that can be determined on little quantities of powder. The compressibility index of the formulation were determined by using following Carr's compressibility index equation.

$$\text{Carr's Compressibility Index (\%)} = \frac{\text{Tapped bulk density- bulk density x100}}{\text{Tapped bulk density}}$$

Relationship between % compressibility and flowability is shown in the following table.

Table 5: Standard values of Carr's index

Carr's Index	**Type of flow**
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Angle of Repose:

It is determined by using the funnel method. The accurately weighed powder is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured to determine the angle of repose.

It was calculated using the following equation.

$$\tan(\theta) = h/r$$

Where 'h' and 'r' are the height and radius respectively of the powder cone

Table 6: Standard values of angle of repose

Flowability	**Angle of repose**
Excellent	<25
Good	25-30
Passable	30-40
Poor	>40

Method of manufacturing dispersible tablets

Direct Compression Method

The Ambroxol Hcl dispersible tablets were prepared by using direct compression method with 9.5mm oval shapes punches and break line on one side of the tablet. The flow chart for direct compression method is given below in following representation.

Flow chart for Ambroxol Hcl dispersible tablets by using direct compression method

Weighing

↓

Sifting

↓

Blending

↓

Lubrication

↓

Tablet Compression

Manufacturing Process

Environment Condition : Room Temperature (25^0C), RH – 65%

Manufacturing Characteristics : machine: Remek – Total 16 stations

Formulation of dispersible tablets ofAmbroxol HCl by using natural gums Karaya gum and Guar gums as super disintegrants.

Method: Direct Compression Method Preparation of Ambroxol hcl (F1- F6) by using direct compression method: Composition of Ambroxol Hcl (F1 – F6):

Table No: 7 Composition of Oral disintegrating tablets of Ambroxol HCl

S.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6
1	Ambroxol HCl	100	100	100	100	100	100
2	Guar gum	6	10	18	-	-	-
3	Karaya gum	-	-	-	6	10	18
4	Microcrystalline cellulose	50	50	50	50	50	50
5	Mannitol	30	26	18	30	26	18
6	Aspartame	10	10	10	10	10	10
7	Magnesium stearate	4	4	4	4	4	4
	TOTAL (mg)	200	200	200	200	200	200

Procedure:

Ingredients such as Ambroxol Hcl was sifted through 24 mesh, Microcrystalline cellulose was sifted through 40 mesh & ingredients such as Guar gum, Karaya gum, mannitol and aspartame, magnesium stearate, talc were passed through 60 mesh. The above ingredients were mixed in double cone blender for 25 mins and lubricants were added to the above ingredients. The lubricated blend was compressed by using oval shaped 9.5 punches.

Evaluation of Ambroxol Hcl dispersible tablets

Physico-Chemical Properties of Tablets[38]:

Hardness:

The hardness of tablets was determined by using Monsanto Hardness tester and it is expressed in Kg/cm^2. The whole experiment was performed in triplicate

Friability:

The friability of the tablet was determined by using Roche friabilator.It is expressed in percentage.Twenty tablets are initially weighed W1 and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes.The tablets were weighed again (W2). The percentage of friability was calculated by using following formula.

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Weight variation:

20 tablets were selected randomly and weighed accurately. The weight divided by 20 provides an average weight of tablets. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than double that percentage. Standard deviation and average weight were calculated

Table 8: Specifications of % Weight Variation Allowed in Tablets as per Indian Pharmacopoeia

Average weight of tablets (mg)	**Maximum percent difference allowed**
80 or less	10
More than80 but less than 250	7.5
250 or more	5

Uniformity of Content:

The drug content in each formulation was determined by mixing 10 tablets and powder equivalent to 10 mg was added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ filter paper, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 246nm.

Disintegration Test:

The test was carried out as per USP- 2008.

One tablet was placed in six tubes of the basket. Phosphate buffer of pH 6.8 is used as the disintegration medium.The temperature of the liquid was maintained at 37^0 c ± 2^0 c. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets, not less than 16 of total of 18 tablets should disintegrate completely.

Wetting time:

A piece of filter paper folded twice and placed in a small petri dish containing 5ml of distilled water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The wetted tablet was then weighed. Wetting time, S, was determined by using following formula.

$$S = 10\times \text{Wb-Wa/Wb}$$

Where, Wa – weight of the tablet before water absorption.

Wb – weight of the tablet after water absorption.

In- Vitro Drug Release Study[39]:-

There are no standard methods yet developed for determining the in vitro drug release for dispersible tablets. The release rate of dispersible tablets of Ambroxol Hcl was carried out using rotating paddle apparatus (USP Type II). The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release study was performed at 37 ^{0}C ± 0.5 ^{0}C with a rotation speed of 50 rpm. The 5ml of sample was withdrawn at time interval of 5, 10, 15,20minutes up to 30 min and replaced with 5 ml of dissolution medium the amount of Ambroxol Hcl released was determined by UV Spectrophotometer at 246 nm.

Table 9: Parameters were used for the dissolution study

Apparatus	**USP Dissolution apparatus (Type II)**
Dissolution medium	Phosphate buffer (pH 6.8)
Temperature	37±0.5 °C
Volume	900 ml
Speed	50 rpm
Sample withdrawn	5 ml
Running Time	30 min

Kinetics of In-vitro Drug Release[40]:

To study the release kinetics of in-vitro drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

Zero order:

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q0 \text{ n } Qt = K0t$$

Rearrangement of equation

$$Qt = Q0 + K0t$$

Where,

Qt - is the amount of drug dissolved in time t,

Q0 - is the initial amount of drug in the solution (most times, Q0 = 0)

K0 - is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

Application:

This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc.

First order:

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation

$$\frac{dC}{dt} = -Kc$$

Where,

K - is first order rate constant expressed in units of time-1.

log C = log C0 n Kt / 2.303

where,

C0 - is the initial concentration of drug

K - is the first order constant

t - is the time in hrs.

The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303.

Application:

This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

Higuchi:

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Huguchi in 1961. Initially conceived for planar systems, it was then extended to different geometrics and porous systems. This model is based on the hypotheses that

Initial drug concentration in the matrix is much higher than drug solubility.

Drug diffusion takes place only in one dimension (edge effect must be negligible).

Drug particles are much smaller than system thickness;

Matrix swelling and dissolution are negligible.

Drug diffusivity is constant.

Perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by the equation:

$$f_t = Q = A\sqrt{D(2C - C_s)\,C_s\,t}$$

Where,

Q- is the amount of drug released in time t per unit area A,

C -is the drug initial concentration,

Cs- is the drug solubility in the matrix media

D- is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

This relation is valid during all the time, except when the total depletion of the drug in the therapeutic system is achieved. To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by equation.

$$f_t = Q = \sqrt{\frac{D\delta}{\tau}(2C - \delta C_s) C_s t}$$

Where,

D- is the diffusion coefficient of the drug molecule in the solvent,

δ -is the porosity of the matrix,

τ -is the tortuisity of the matrix.

Q, A, Cs and t have the meaning assigned above.

Tortuisity is defined as the dimensions of radius and branching of the pores and canals in the matrix. In a general way it is possible to simplify the Higuchi model as generally known as the simplified Higuchi model.

$$f_t = Q = K_H \times t^{1/2}$$

Where,

KH is the Higuchi dissolution constant. The data obtained were plotted as cumulative percentage drug release versus square root of time.

Application:

This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

Korsmeyer Peppas:

Korsmeyer et al. (1983) derived a simple relationshipwhich described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer Peppas model.

$$M_t / M_\infty = Kt^n$$

Where,

Mt / M∞ - is a fraction of drug released at time t,

k- is the release rate constant and n is the release exponent.

The n value is used to characterize different release for cylindrical shaped matrices.In this model, the value of n characterizes the release mechanism of drug as described should only be used. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickian diffusion. If n < 0.5 the mechanism is quasi-Fickian diffusion, and 0.5 < n < 1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion, n> 1.0 mechanism is non Fickian super case II.

Stability Study[41]:

Stability Studies:[29]

Introduction

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. In addition, product-related factors influence the stability, e.g. the chemical and physical properties of the active substance and the pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system, and the properties of the packaging materials. Also, the stability of excipients that may contain or form reactive degradation products, have to be considered.

Table- 10: Objectives of Stability Testing:

OBJECTIVE	**TYPE OF STUDY**	**USE**
To select adequate (from the viewpoint of stability) formulations and container-closure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-	Real-time	Registration dossier

life		
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real- time	Qeleuality assurance in general, including quality control.

Climatic Zones and Conditions

WHO has issued guidelines, where it is stated that the world is divided into four zones based on the prevailing annual climatic conditions for the purpose of stability testing.

Zone I: temperate

Zone II: subtropical with possible high humidity

Zone III: hot/dry

Zone IV: hot/humid

Table-11: Mean climatic conditions: measured data in the open air and in the storage room

Climatic Zone	**Measured data in the Open Air**		**Measured data in storage room**	
	^{o}C	**%RH**	**^{o}C**	**%RH**
I	10.9	75	18.7	45
II	17.0	70	21.1	52
III	24.4	39	26.0	54
IV	26.5	77	28.4	70

So for example if a manufacturer plans to sell his products in zone-III he/she should do real time studies at 30^{o}C and 35%RH.If a manufacturer wants to apply for the registration of a new drug, i.e. if he is applying for a (1) Investigative New Drug Application (IND) or (2) New Drug Application (NDA) or (3) Abbreviated New Drug Application (ANDA) then he has to assure the FDA regarding the drug's/drug product's safety, quality and efficacy. For this he has to carry out stability tests and submit stability data. How he should do this is specified by Q1A (R2).

Selection of Batches

Data from formal stability studies should be provided on at least three primary batches of the drug substance. These batches should be made to a minimum of pilot scale by the same synthetic route as that of the production batches.

Specifications which include testing methods and acceptance criteria should be fixed.

Testing frequency in Months

Long term: 0, 3, 6, 9, 12, 18, 24

Accelerated storage: 0, 3, 6

Storage conditions recommended

Table-12 : Testing frequency for different storage conditions

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term*	$25^0C + 2^0C/60\%$ RH + 5% RH or $30^0C + 2^0C/65\%$ RH + 5% RH	12 months
Intermediate**	$30^0C + 2^0C/65\%$ RH + 5% RH	6 months
Accelerated	$40^0C + 2^0C/75\%$ RH + 5% RH	6 months

* It is up to the applicant to decide whether long term stability studies are performed at 25 + 2°C/60% RH + 5% RH or 30 ^{0}C + 2°C/65% RH + 5% RH.

** If 30°C + 2°C/65% RH + 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C+ 2°C/60% RH + 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria (ICH, 2003)

"Significant change" for a drug substance is defined as failure to meet is specification.

Table -13 : Drug substances intended for storage in a refrigerator

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	5^0C + 3^0C	12 months
Accelerated	25^0C + 2^0C/60% RH + 5% RH	6 months

Table-14 : Drug substances intended for storage in a freezer

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	20^0C + 5^0C	12 months

Stability Testing for Established Drug Substances

WHO has issued guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage form. The stability of finished pharmaceutical products depends on environmental factors and on product related factors. So stability considerations should be given, the highest priority in the design and formulation of a product. The shelf life should be established with due regard to the climatic zones. To ensure both patient safety and the rational management of drug supplies, it is important that the expiry date and storage conditions are properly indicated on the label.

Accelerated stability testing

These are the studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from real – time stability studies, may be used to assess longer – term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes. These are also known as stress testing studies.

Expiry date

The date given on the individual container of a drug product up to and including which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life period to the date of manufacture.

Real time (Long term) stability studies:

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf life, to confirm the projected shelf life and to recommend storage conditions.

Stability testing is an integral part of formulation development. It generates information on which to base proposals for the shelf lives of drug substances and products and their recommended storage conditions. Stability data also are a part of the dossier submission to regulatory agencies for licensing approval.

Stability testing ensures that a drug substance will be safe and effective throughout the shelf life of the product. However, meeting the potency and purity profiles established in the compendia can be challenging as pharmaceutical products become increasingly complex and diverse.

The optimized formulation F3 packed in PVC blister pack then, they were stored at three different temperatures $4^0C \pm 2^0C$, $27^0C \pm 2^0C$ and $45^0C \pm 2^0C$ for 45 days at RH 75±5%. At 15 days intervals, the tablets were evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time.

5. RESULTS AND DISCUSSION

5.1 Identification of Drug:

Organoleptic properties:

Colour: White or slightly yellow.

Odour: Odourless.

Taste: Tasteless.

Nature: crystalline powder.

5.2Melting point:

232.7^{o}c

5.3 Solubility study:

Sparingly soluble in water,Soluble in methyl alcohol,Practcally iinsoluble in methylene chloride

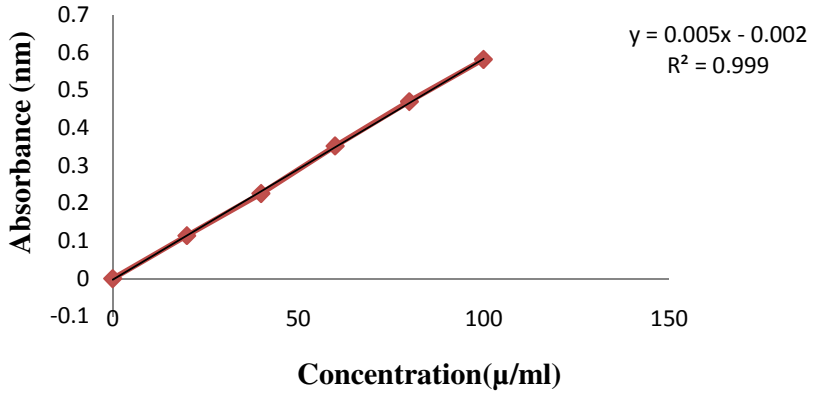
5.4 standard calibration curve of Ambroxol Hcl

Serial of dilutions are made from standard working solution with distilled water to get concentration from 20 to 100 microgram / ml and the absorbance was measured at 246nm.

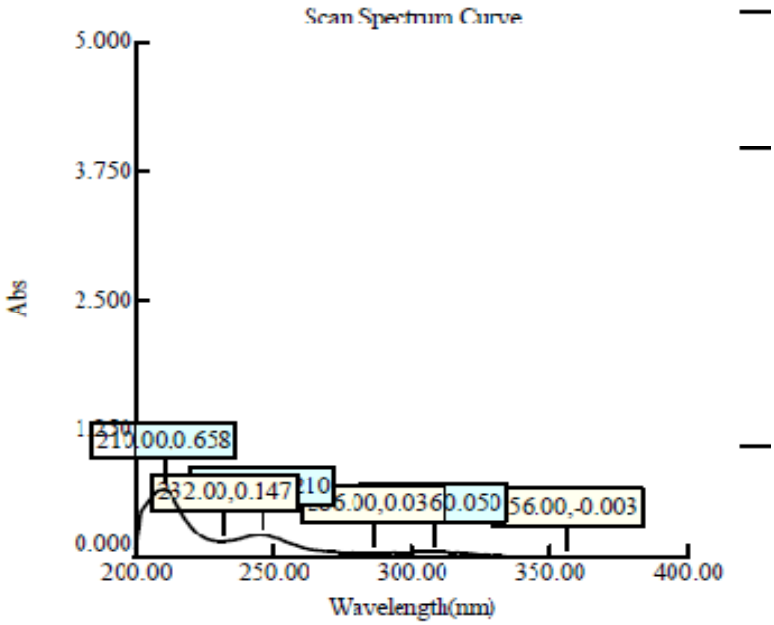
Table No: 15 Standard Calibration curve of Ambroxol Hydrochloride

S.No	Concentration (mcg/ml)	Absorbance
1	20	0.114
2	40	0.226
3	60	0.352
4	80	0.470
5	100	0.582

Graph 1:Standard graph of Ambroxol Hcl



Graph 2: lambda max of Ambroxol Hydrochloride



Instrument Performance

Model : UV-VIS Spectrophotometer
Number : 19-1885-01-0126
Spectral Bandwidth : 2.00 nm

Scan Spectrum Performance

Scan Range : 200.00 to 400.00 nm
Measure Mode : Abs
Interval : 2.00 nm
Speed : Fast
Data File : Untitled1.spd
Create Date/Time : Saturday, December 07, 2013 11:49:55 AM
Data Type : Original
Method File:

No.	P/V	Wavelength(nm)	Abs	Comment
1	Peak	308.00	0.050	
2	Peak	246.00	0.210	
3	Peak	210.00	0.658	
1	Valley	356.00	-0.003	
2	Valley	286.00	0.036	
3	Valley	232.00	0.147	

5.5 FTIR studies:

INFRA RED SPECTRUM OF PURE AMBROXOL HCL

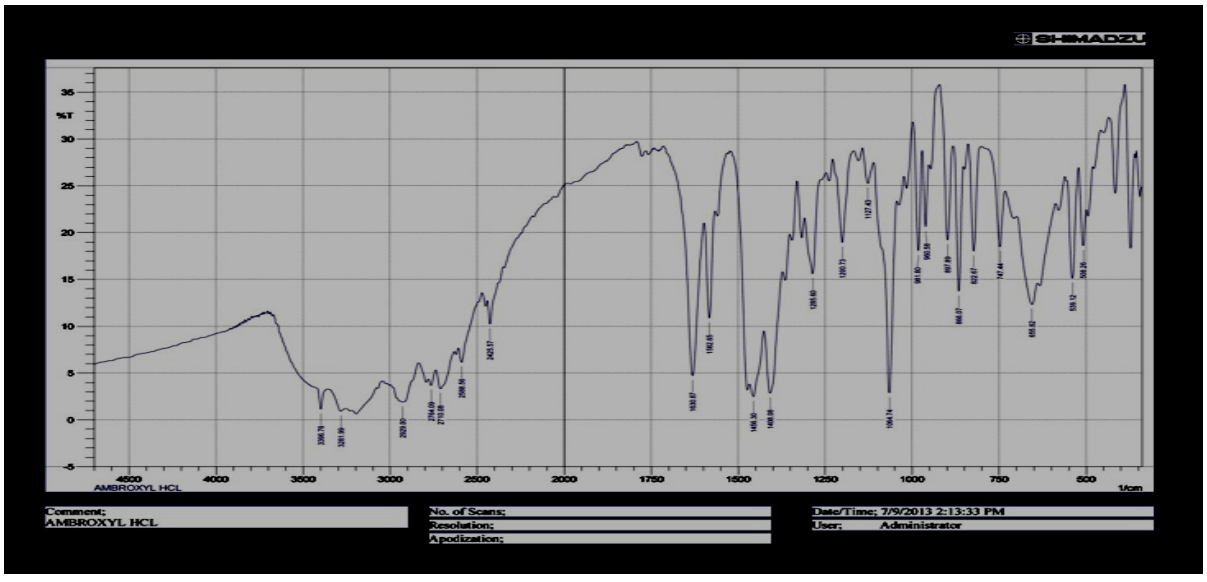


Fig-6

INFRA RED SPECTRUM OF AMBROXOL HCL WITH KARAYA GUM

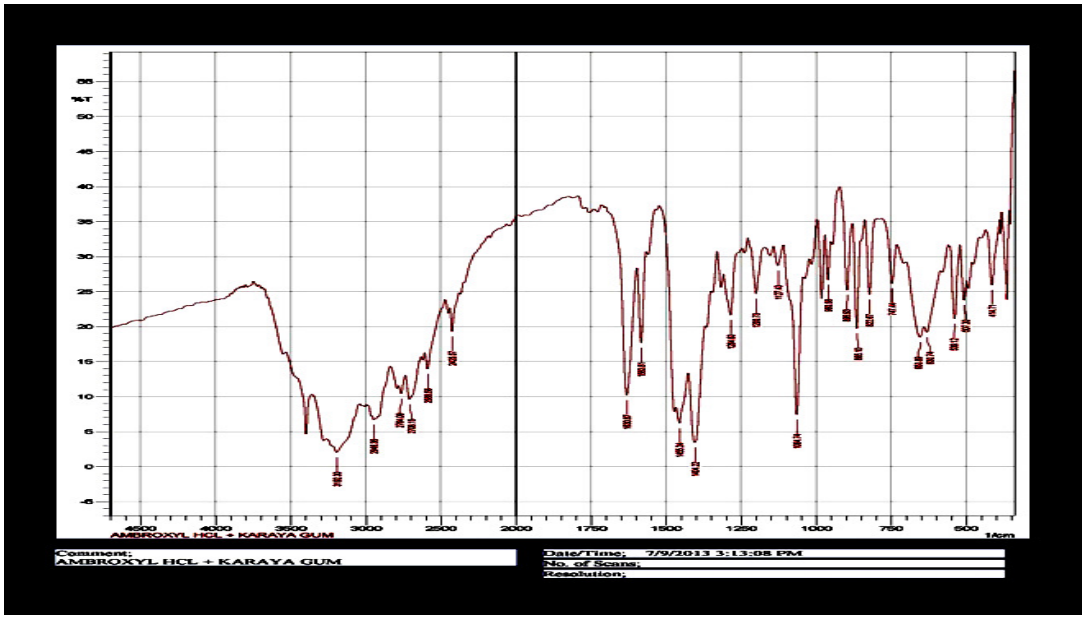


Fig-7

INFRA RED SPECTRUM OF AMBROXOL HCL WITH GUAR GUM

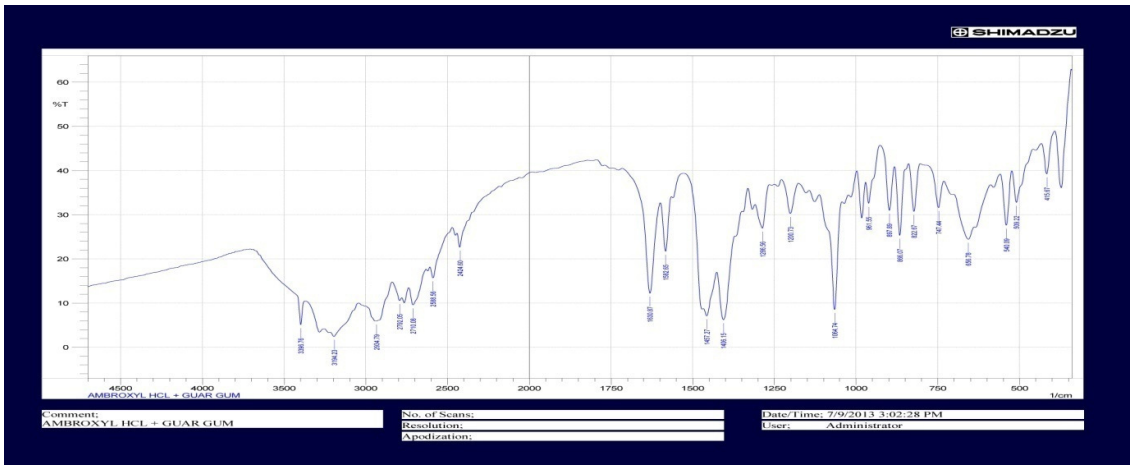


Fig-8

INFRA RED SPECTRUM OF AMBROXOL HCL WITH MICRO CRYSTALLINE CELLULOSE

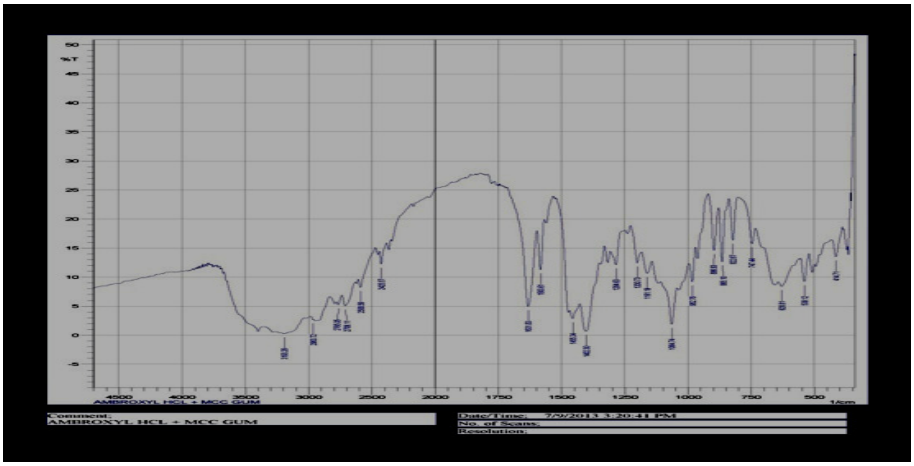


Fig-9

INFRA RED SPECTRUM OF AMBROXOL HCL WITH MICRO CRYSTALLINE CELLULOSE

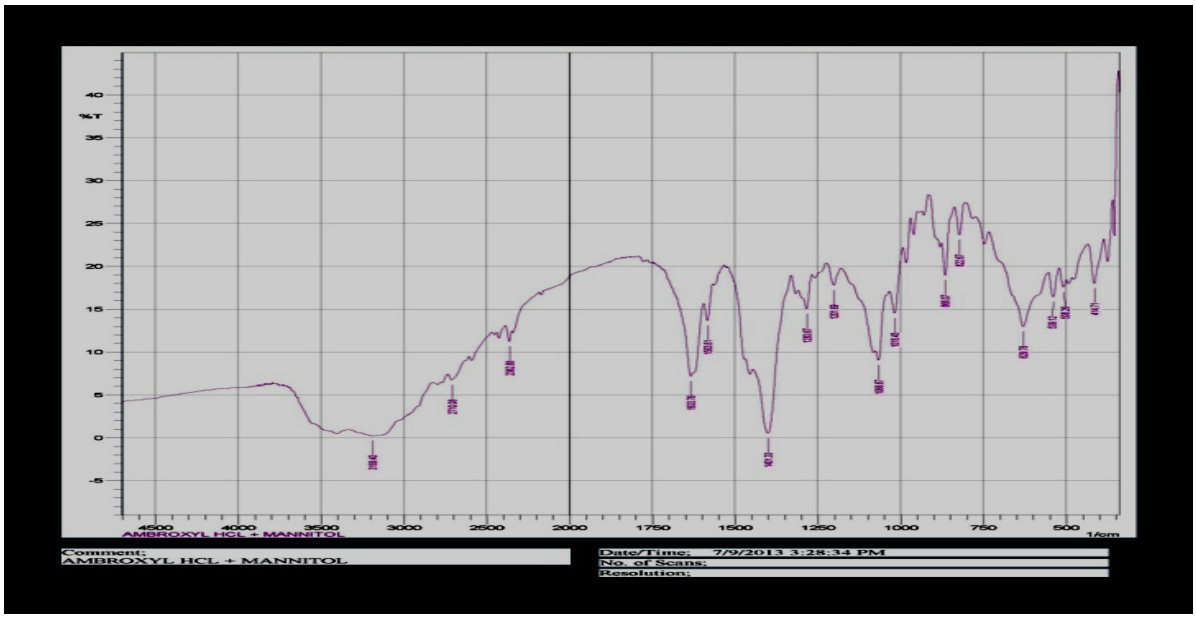


Fig -10

Table: IR characteristic functional groups of pure drug and Drug polymer mixture:

Functional groups	Drug	Drug + polymer
NH2 Stretch	3396.76	3396.76
N-H Stretch	3281.99	3281.99
CH2 Stretch	2929.00	2934.79
OH Stretch	3196.10	3194.23
CH=CH stretch	3055.33	3054.31
CN Stretch	1457.27	1457.27

IR spectra of pure Ambroxol HCl showed the major bands .From the above table and figures 6-10, it can be seen that, the major functional group peaks observed in spectras of Drug with all the polymers remains unchanged as compared with spectra of Ambroxol Hcl. So from the above IR spectra it can be observed that there is no interaction between Ambroxol Hcl and Polymers used in the formulations.

5.6 Micromeritic properties to the Ambroxol oro dispersible tablets:

The results of the Micromeritic properties of the granules are presented in table No: 16.

Table No: 16 Micromeritic properties of Ambroxol HCl Dispersible tablets

Form. No	Angle of repose (θ°)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressi-bility Index (%)	Hausner Ratio
F1	22.33	0.425	0.464	8.60	1.094
F2	22.29	0.416	0.459	9.36	1.103
F3	24.15	0.425	0.465	8.60	1.094
F4	23.48	0.421	0.459	8.27	1.090
F5	25.26	0.431	0.470	9.57	1.105
F6	22.78	0.425	0.481	10.60	1.118

The Bulk density of various powder mixed blends prepared with different superdisintegrants, was measured by graduated cylinder. The bulk density was found in the range **0.416– 0.431 kg/cm^3.**

The Tapped density of various powder mixed blends prepared with different superdisintegrants, was measured by graduated cylinder. The Tapped density was found in the range **0.459– 0.481 gm/cm^3.**

The Compressibility index of various powder mixed blends, prepared with different superdisintegrants, using bulk density and tapped density data, compressibility index was calculated. It was found in the range **8.27 – 10.60%.**

The Hausner's ratio of various powder mixed blends, prepared with different superdisintegrants, using bulk density and tapped density data, Hausner's ratio was calculated. It was found in the range **1.090 – 1.118.**

Angle of repose ranged from **22.29-25.26.** The flow properties of powder blend in all formulations exhibit good flow characteristics.

5.7 Appearance of the tablet:

White colored, oval uncoated, molted tablet with plain surface on two side.

5.8 Physical Evaluation of the Ambroxol Hcl orodispersible tablets:

The result of the Physico-chemical properties of the prepared tablets was done as per the procedure and presented in the table no: 17.

Table No -17 Physical Evaluation of the Ambroxol Hcl orodispersible tablets

For m. No	Weight variation in mg	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (min)	Uniformity of content	Wetting time (sec)
F1	202±7.5	3.50	0.293	1.20	Pass	54.55
F2	200±7.5	3.48	0.293	1.09	Pass	55.86
F3	201±7.5	3.42	0.291	1.04	Pass	54.47
F4	205±7.5	3.58	0.428	1.25	Pass	56.37
F5	199±7.5	3.68	0.426	1.19	Pass	59.35
F6	200±7.5	3.71.	0.426	1.13	Pass	54.29

Evaluation of Ambroxol Hcl tablets:

Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications, less than **5%.**

Tablets were evaluated by using Vernier calliper. The thickness of the tablets was found in the range **5.2 – 6.0 mm**. Uniformity thickness was obtained due to uniform die fill. Tablets were evaluated by using Pfizer Hardness tester. Hardness of the tablets was found in the range **3.36 – 3.71 Kg/cm^2.** Uniform hardness was obtained due to equal compression force.

Tablets were evaluated by using Roche Friabilator and friability of tablets was observed in the range **0.291 - 0.530.**

Tablets were evaluated for disintegration time in the IP disintegration apparatus. The disintegration time was found in the range **29 – 33 sec.**

The tablets are evaluated for the uniformity dispersion in which all the tablets were dispersed in few seconds in purified water and all the formulations were under the IP limits.

Tablets were evaluated for wetting time test. The wetting time was found in the range **54 – 59 sec.**

Tablets are evaluated for the content uniformity test all the formulations are under the IP specifications

5.9 Assay of prepared Ambroxol dispersible tablets:

The results of the assay of Ambroxol Hcl were done as per procedure and presented in the table no: 18.

Table No: 18 Assay of prepared Ambroxol dispersible tablets

Formulation No	**Assay of Ambroxol Hcl in % w/w**
F1	98.3
F2	98.6
F3	99.0
F4	101.7
F5	101.5
F6	102.2

Tablets were evaluated by using assay method. The drug was obtained in the acceptable limit. The drug content was found in the range **98.3 – 102.2%.**

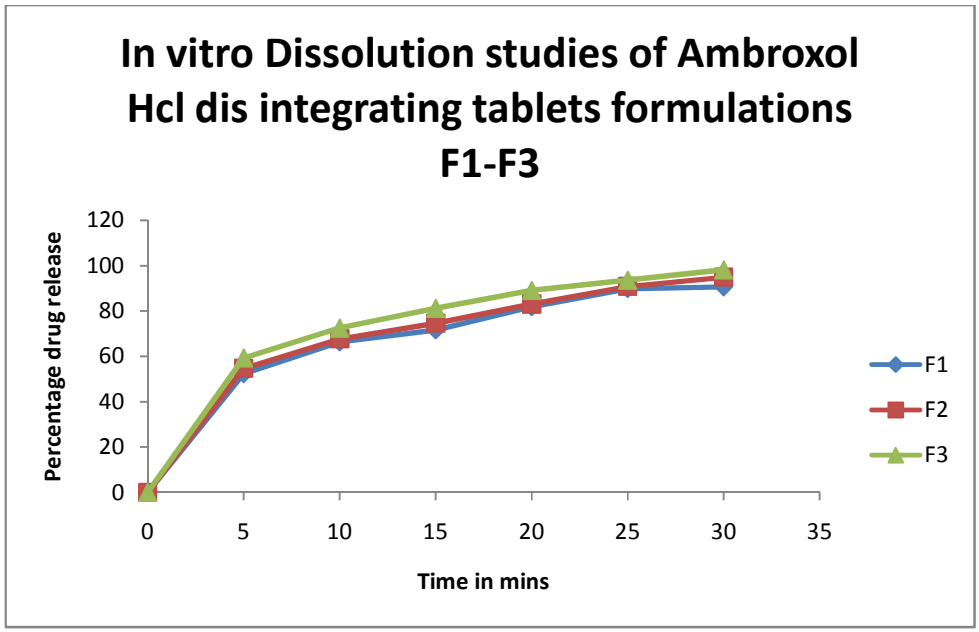
5.10 In–vitro drug release studies

In–vitro drug release of Ambroxol HCl

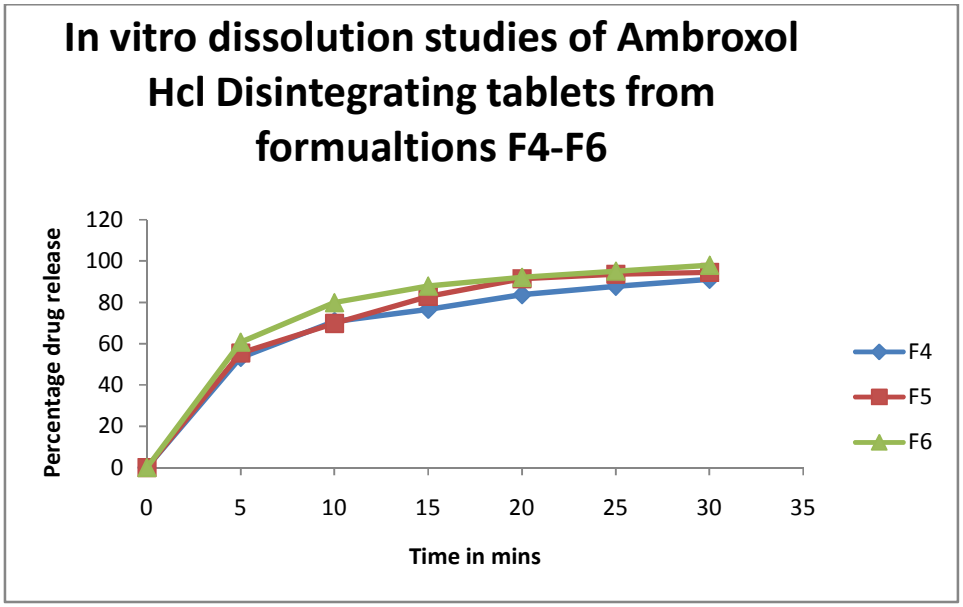
Table No: 19: In Vitro Dissolution Profile of Ambroxol Hcl dispersible tablets in pH6.8 Buffer Solution

Time in mins	F1	F2	F3	F4	F5	F6
5	52.45	54.78	59.31	53.28	55.46	60.71
10	66.44	67.80	72.54	70.78	69.80	79.88
15	71.70	74.70	81.20	76.54	82.88	87.91
20	81.89	83.10	89.13	83.72	91.43	92.14
25	89.92	90.89	93.67	87.78	93.58	95.13
30	90.71	94.97	98.21	91.12	94.45	97.99

Graph 3: In vitro Dissolution studies of Ambroxol Hcl dis integrating tablets formulations F1-F3



Graph 4: In vitro Dissolution studies of Ambroxol Hcl dis integrating tablets formulations F4-F6



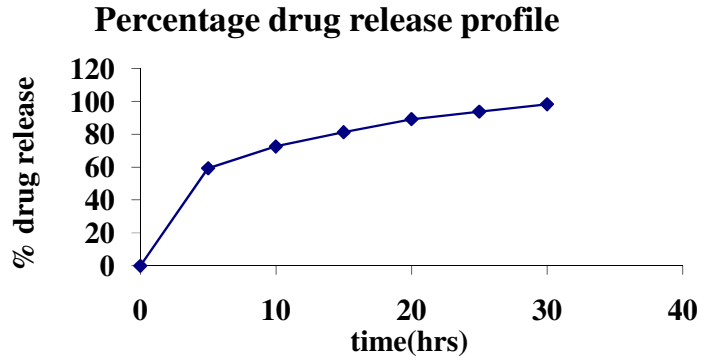
Invitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 50 rpm. The percentage drug release at the end of 30 min was found in the range **90 – 98 %.**

5.11 Kinetics study:

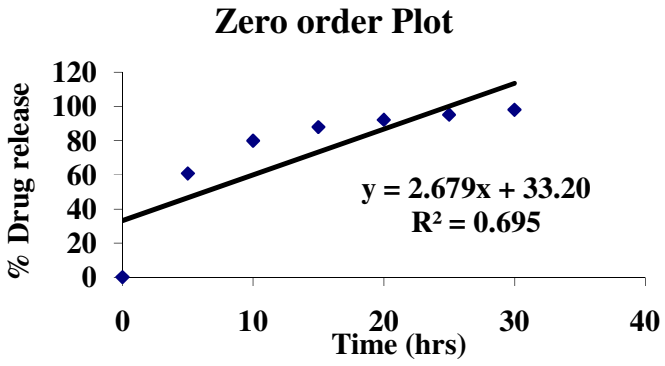
Table 20: Dissolution Kinetics of optimized batch F6.

TIME	SQRT	LOG TIME	% DRUG REL	LOG % D REL	% D REM	LOG % D REM
0	0	#NUM!	0	#NUM!	100	2
5	2.236068	0.69897	59.31	1.7731279	40.69	1.60948769
10	3.162278	1	72.54	1.8605776	27.46	1.438700533
15	3.872983	1.176091	81.2	1.909556	18.8	1.274157849
20	4.472136	1.30103	89.13	1.9500239	10.87	1.036229544
25	5	1.39794	93.67	1.9716005	6.33	0.80140371
30	5.477226	1.477121	98.21	1.9921557	1.79	0.252853031

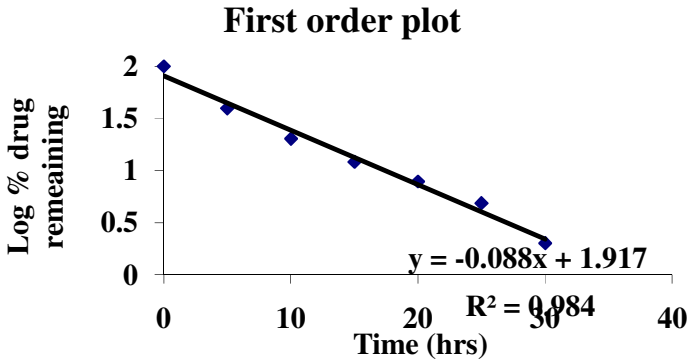
Graph 5: Percentage drug release profile



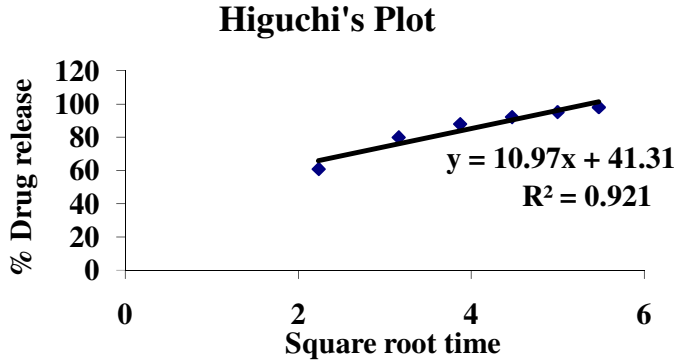
Graph 6: Zero order plot



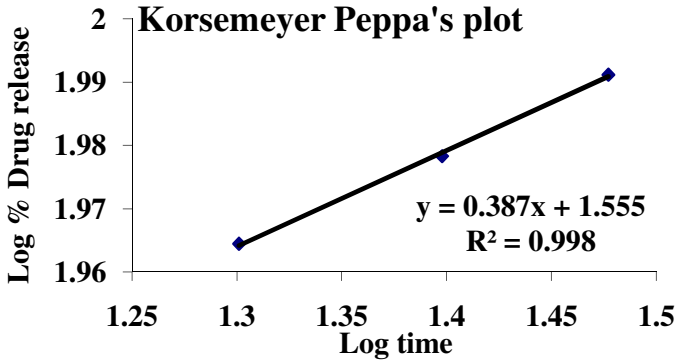
Graph 7: First order drug profile



Graph 8: Higuchi's plot



Graph 9: Peppa's korsemeyer's plot



Graph 10

Discussion:

The release profile of the optimized formula F6 fitted best to Korsmeyer-Peppas model with R^2 value of 0.998. As the n value for the Korsmeyer-Peppas model was found to be less than 0.45, it follows Fickian transport.

5.12 Stability studies:

Table 21: Stability studies of Ambroxol Hcl oro dispersible tablets.

Parameters	After 15 days	After 30 days	After 45 days
Physical appearance	No change	No change	No change
Weight variation (mg)	201±3.34	199±2.55	199±4.23
Hardness (kg/cm^2)	3.42±0.23	3.30±0.64	3.25±0.99
Friability (%)	0.29±0.05	0.31±0.08	0.32±0.06
Drug content (%/tablet)	99.00±0.34	98.81±0.29	98.01±0.87
Wetting time (sec)	54.47±0.41	55.12±0.15	56.51±0.59
Disintegration time (sec)	29.25±0.15	31.13±0.45	35.05±0.61
Percentage drug release	98.21±0.96	95.36±0.19	85.15±0.15

Discussion:

According to ICH guidelines, 45 days stability study at 4^0C ±2^0C, 27^0C ±2^0C and 45^0C ±2^0C for 45 days at RH 75±5% of optimized formulation (F6) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 4^0C ±2^0C, 27^0C ±2^0C and 45^0C ±2^0C for 45 days at RH 75±5% for 45 days.

6. SUMMARY AND CONCLUSION

The study was carried to formulate and evaluate dispersible tablet dosage form containing Ambroxol Hcl as a mucolytic drug.

The present study is an attempt to select best possible combination of diluents and disintegrants to formulate dispersible tablet of Ambroxol Hcl which disintegrates within few minutes there by reducing the time of onset of action.

Mannitol is selected as diluents, natural gums such as guar gum, Karaya gum were selected as super disintegrants. Microcrystalline cellulose was used in all formulations. Aspartame as a sweetening agent, Magnesium stearate as a Lubricant.

Guar gum is used as the super disintegrant in the formulation F1 – F3 at the concentrations of the 6, 10, 18 % respectively.

Karaya gum is used as the super disintegrant in the formulation F4 – F6 at the concentrations of 6, 10, 18 % respectively.

Direct Compression method was used to formulate the tablets.

All the formulations were showed the acceptable flow properties and the precompression parameters like Bulk density, Tapped density and Hausner ratio.

The post compression parameters like Hardness, Friability, Disintegration time, Weight variation, wetting time, Dispersion time values were found to be within the IP limits.

The percentage Drug content of all tablets was found to be between 98.3% - 102.2% of Ambroxol Hcl , which is within the limit.

As the concentrations of the guar gum increases in the formulations F1 – F3 the disintegration time found to be decreased and the disintegration time for these formulations were 1.20, 1.09, 1.04 seconds respectively and the percentage drug release was also found to be increased for these formulations as 90.71, 94.97, and 98.21 % respectively. From the above results it was found that as the concentration of guar gum increased and microcrystalline cellulose decreases the disintegration and dissolution time was found to be improved, so considering the above results it was found that the F3 batch was found to be optimized batch and it pass all the preformulation parameters and evaluation results as per the IP limits

From the data obtained, it is observed from the formulation containing Guar gum - 18mg, Micro crystalline cellulose - 50mg in **Formulation F3**, shows Disintegration time in 1.04 mins and the Percentage drug release is of 98.21 % at the end of 30 min which satisfied all the tablet evaluation parameters for dispersible tablet. Hence looking at all the satisfactory parameters F3 batch is selected as the optimized batch.

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